AMERICAN HEART JOURNAL

October, 1959
Volume 58, No. 4

Editorial

Some Metabolic and Structural Characteristics of Experimental Nephrosis

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Nephrosis was first experimentally reproduced by Masugi,[1] in 1933, by means of an antiserum against rat kidney produced in the rabbit. When the antiserum is injected into the rat its nephrotoxic effect results from an antigen-antibody reaction, as evidenced by a fall in complement[2] and a localization of antibody in the renal glomerulus.[3] The specific site of glomerular localization, and therefore by inference the localization of the specific antigen or antigens, is in or on the glomerular basement membrane.[4,5] There are multiple glomerular antigens[6] which are identical with, or closely related to, antigens present in extraglomerular tissues. These antigens are present in various tissues in proportion to the degree of vascularity of the tissue and are presumed to be associated with the basement membrane of precapillary, capillary, and postcapillary vessels.[5,7] Since the clinical picture of hyperlipemia, hypoproteinemia, proteinuria, and anasarca resulting from the antibody localization is referable to the kidney, it may be inferred that the basement membrane subserves its most vital role in that location.

A similar type of disease can be produced in the rat by the daily subcutaneous injection of 6-dimethylamino-9-(3′-amino-3′-deoxy-b-D-ribofuranosyl) purine, the aminonucleoside derivative of the antibiotic, Puromycin.[8] The aminonucleoside disease occurs after the latent period of 5 to 15 days, depending on dosage.[9] Following the daily administration of 0.015 mg. of aminonucleoside per gram of rat the animals usually die on about the sixteenth day. With the same dosage it has been found that the disease regresses if the injections are terminated on about the fourteenth day.[10] In addition to the in vivo toxicity of this compound both the aminonucleoside and the antiserum against rat kidney have cytotoxic effects on tissue cultures of rat kidney.[11,12]

Examination of kidney sections with the light microscope reveals that in the lipoid nephrosis of children, and in both varieties of experimental nephrosis discussed here, a thickening of the basement membrane, an increased number of

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Received for publication June 19, 1959.

PAS positive droplets in the proximal convoluted tubules, and a decrease in alkaline phosphatase in the tubules occur.[13-15] Electron microscopic studies of kidney sections also show identical changes in the lipoid nephrosis of children and in the aminonucleoside nephrosis. These changes consist of swelling and coalescence of the foot processes of the epithelial cells covering the glomerular basement membrane, and an increase in the number and size of the cytoplasmic vacuoles within these cells.[10,16,17] In animals recovering from the aminonucleoside nephrosis the pathologic changes observable with the electron microscope show beginning regression.[10] This may be compared with the observation that in the human nephrotic syndrome, steroid therapy reverses the changes in the foot processes.[18,19] The electron microscopic studies both in the lipoid nephrosis of children[16,17] and in the aminonucleoside disease[10] indicate that the first morphologic changes occur in the epithelial cells at the same time as the onset of the severe proteinuria. Later in the development of the disease there is an increase in the amount of the basement membrane material and an increased number of endothelial cell nuclei. It has also been reported that defects measuring several hundred to 1,000 Å were found in the glomerular basement membrane of a patient with nephrosis.[20] The primary change in the morphology of the epithelial cell component of the renal corpuscle is also reflected in the abnormal presence of alkaline phosphatase in these cells in the antibody-induced nephrosis.[21] Later in the course of the disease the basement membrane and the endothelial cells also become alkaline-phosphatase positive, whereas the tubular cells have a decreased concentration of this enzyme. The latter event is probably coincidental to the loss of the brush border.[17]

The ability of the aminonucleoside to reproduce so exactly the same pathologic picture found in the nephrotic disease of children and in the antigen-antibody disease produced in rats has provided a convenient tool with which to study the possible mechanism by which such a disease process might occur. Since there is a marked structural resemblance between the aminonucleoside and adenosine, the possibility was considered that the aminonucleoside might act as an inhibitor in the formation of, or in reactions involving, ATP, or in some other phase of nucleotide metabolism. If such were the case, administration of various purine derivatives might prevent the inhibition. Adenine and a number of synthetic purine derivatives were known to reverse the antitrypanosomal action of the aminonucleoside in mice,[22] and more recently it was established that the aminonucleoside inhibits the formation of ATP from inorganic phosphate and adenosine by brewer's yeast.[23] The data obtained to date[24] support the idea that the aminonucleoside acts as an antimetabolite during the production of the nephrotic syndrome in rats. When given simultaneously with the aminonucleoside, adenine partially inhibited the development of the nephrosis, whereas adenosine, in the doses given, did not. The failure of adenosine was probably due to the high level of adenosine deaminase present in mammalian tissues.[25] The picture is complicated by the fact that adenine is toxic and can produce thickening of the basement membrane.[24]

The possible practical implications of these experimental observations revolve on either or both of two premises: (1) In the human patient with nephrosis

there may exist at some time during the onset of his disease either an abnormal nucleotide or nucleoside which functions as an antimetabolite, or a normal nucleotide or nucleoside which is present in abnormally high concentrations and serves as an inhibitor of sensitive enzyme systems. (2) The morphologic common denominator of nephrosis is injury to a specific component of the renal corpuscle. At the present time there is no evidence for the existence of a specific antimetabolite which may give rise either to the allergic experimental nephrosis or to human nephrosis. However, because of the marked resemblance between the antibody-induced nephrosis and the aminonucleoside nephrosis the possibility cannot be discounted that some substance which functions as an antimetabolite may be formed as a by-product of the antigen-antibody reaction. Currently, the only link between renal disease and aberrant purine metabolism is a preliminary report showing that the blood of azotemic patients contains an abnormally high level of nucleotides. In this study the greatest increase was in ATP, but increases were also found in DPN, TPN, and GTP.[26] There is a gradually accumulating body of evidence that the epithelial cell is the primary site of damage in both human and experimental nephrosis.[10,16,17] That a chemical agent causing this damage might exert its effect in some phase of nucleotide or nucleic acid metabolism is an enticing concept which deserves further consideration and investigation.

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Clinical Communications

The Diastolic Pressure Gradient Between the Left Atrium and the Left Ventricle in Cases of Mitral Stenosis

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During the years 1953-1957, we routinely carried out left heart catheterizations on patients with mitral valvular disease who were to undergo surgical treatment at the Sabbatsbergs Hospital in Stockholm. We then tried to measure the diastolic pressure on each side of the mitral valves. Because of our limited laboratory resources we could only measure the blood flow at the same time in a small number of cases. We report here the results of these investigations in 63 patients with mitral valvular disease. All of these patients were operated upon, and thus, the degree of stenosis and regurgitation through the mitral valve has been verified.

METHOD

The left atrium was punctured paravertebrally from the right side above the ninth rib, according to Björk.[1-3] A thin plastic catheter was introduced through the needle into the left atrium and then further introduced through the mitral ostium down into the left ventricle, and in many cases it was then also advanced out through the aortic ostium into the root of the aorta. Pressure measurements were made through the plastic catheter, which was kept open by intermittent flushing with a solution of 0.1 per cent heparin in saline solution. The pressure measurements were first performed with the Thybjerg-Hansens capacitance manometer. For practical reasons we then changed to the Statham pick-up type (P23D), with an alternating-current magnifier, Type EMT-460 (Elema, Stockholm). In all cases the Elema apparatus for optic registration of the pressure curves was used. The method used, and its risks and complications were described in an earlier publication.[6]

THE PRACTICAL RESULT OF THIS METHOD

Puncture of the left atrium, according to Björk, has always been successful. In a series of 159 patients, there were only two occasions on which the left atrium

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Received for publication May 27, 1959.

was not reached at the first attempt, and the reasons preventing another trial differed. It was then possible in 92 per cent of the cases to push the plastic catheter down from the left atrium into the left ventricle. The cases in which it was not possible to get the catheter down into the ventricle were those in which there was a very large left atrium in which the soft plastic catheter rolled up without passing the mitral ostium. Also, cases in which there was significant regurgitation fell into this group; in these the plastic catheter could not be passed into the left ventricle because the regurgitant jet, time after time, threw the catheter back into the left atrium, after the registration of that pressure had proved a few beats of left ventricular type. This was such a constant finding that it was considered to be diagnostic. In 40 per cent of the cases in which the catheter was introduced into the left ventricle it could also be pushed out into the root of the aorta.

Perfect pressure curves were not obtained in all cases in which the catheter was passed down into the left ventricle. This was especially so in those cases in which the left atrium was very large and some time was needed to manipulate the catheter down into the ventricle. In spite of the intermittent flushing through the catheter, small coagula in the orifice of the plastic catheter caused damping of the pressure curves. In a few other cases the catheter became kinked or rotated around its long axis during the manipulations required to push it down into the left ventricle, causing a significant damping of the curves. Then it was considered too complicated to change the catheter. The needle and its catheter should be withdrawn simultaneously in order to avoid cutting off the catheter against the sharp edge of the needle. After the needle has been withdrawn it would be necessary to puncture the left atrium again, which is not recommended, because too many punctures will increase the risk of hematopericardium.

In some patients the registered pressure curves were not considered to be representative because there had been a fall in blood pressure during the investigation. The causes of failure to register the diastolic pressure on both sides of the mitral orifice can therefore be summarized as follows: (1) The catheter could not be introduced into the left ventricle in 8 per cent. (2) The pressure curves obtained were too damped in 12 per cent. (3) Blood pressure fell to a systolic value of below 90 mm. Hg in 7 per cent. (4) Blood pressure fell to a systolic value of 100 to 91 mm. Hg in 6 per cent. (Total, 33 per cent of the cases.) Thus, in a third of the cases undergoing left heart catheterization we have not been able to obtain perfect pressure curves permitting a calculation of the pressure gradients across the mitral orifice.

MATERIAL

Sixty-three patients with a varying degree of mitral stenosis were submitted to left heart catheterization for the evaluation of surgical treatment. The material will therefore represent cases in which the physician, on the basis of the data obtained during physical examination, roentgenologic and electrocardiographic investigation, considered the stenotic component in the mitral valve to be the dominant lesion. In all of these cases a withdrawal curve from the left ventricle to the left atrium was registered, and in all the diagnosis was verified by surgery.

In 35 patients a pure mitral stenosis was observed; in 21 patients there was a dominating mitral stenosis with a concomitant regurgitation; and in 2 patients there was a dominating mitral regurgitation with a smaller mitral stenosis. One patient had a mitral stenosis and a concomitant atrial septal defect, 2 patients had a mitral stenosis with concomitant aortic valvular lesion, and in 2 patients the mitral stenosis could not be classified because of the inadequate operative notes (see Table I).

TABLE I. OPERATED CASES OF MITRAL STENOSIS WITH A DIASTOLIC LEFT ATRIUM-LEFT VENTRICULAR PRESSURE GRADIENT

DIAGNOSIS	NUMBER OF CASES
Pure mitral stenosis	35
Dominating mitral stenosis + concomitant mitral regurgitation	21
Mitral stenosis + atrial septal defect	1
Dominating mitral stenosis + aortic lesion	2
Dominating mitral regurgitation + mitral stenosis	2
Mitral stenosis, not classified	2
Total	63

Verification of the Diagnosis at Surgery.—The diagnosis in all cases was verified by the surgeon during the intracardiac palpation of the mitral orifice, and in a few cases, by direct inspection of the mitral valves. Naturally, this control at surgery also has some faults. (1) It is difficult for the surgeon to give an absolutely exact description of the opening in the mitral ostium by blind intracardiac palpation, which has usually been the case in this material. (2) It is still more difficult to evaluate and grade the regurgitant component. Of course it is possible to decide whether there is a regurgitant jet or not, but it is more difficult to ascertain whether it is a thin regurgitant jet, or whether a regurgitation is encountered along a greater part of the orifice. We have tried to evaluate the regurgitation by the distance behind the mitral orifice that the regurgitant jet can be palpated in the left atrium. This method will give some information about the degree of regurgitation, but can, of course, not give any exact opinion about the degree of the stroke volume going back into the left atrium. (3) In a few cases the operating notes have not been carefully written about the degree of regurgitation.

Evaluation of the Pressure Gradient.—The pressure gradient was calculated from withdrawal curves recorded when the plastic catheter was slowly drawn from the left ventricle into the left atrium. The difference in pressure was measured in millimeters of mercury between the left atrium and left ventricle immediately before the rise in pressure due to the left atrial contraction (the *a* wave) in cases with sinus rhythm, and immediately before the pressure wave (*c* wave) caused by the closure of the mitral valves in cases with auricular fibrillation. This value was then compared with the end-diastolic left ventricular pressure. This end-diastolic pressure was calculated immediately before the rapid rise in pressure due to the isometric contraction in cases of auricular fibrillation.

On the other hand, in cases with sinus rythm, the pressure wave transmitted from the auricular systole was transmitted into the left ventricular pressure curve as a slight presystolic rise in pressure immediately before the rapid rise in pressure due to the isometric contraction. In these cases the calculation was made in the beginning just before the presystolic rise in pressure.

RESULTS (SEE TABLES II AND III)

1. In the 56 patients having a mitral lesion the left atrial pressure varied between 37 and 6 mm. Hg, with a mean pressure of 21.9 ± 1.1 mm. Hg. There was a pure mitral stenosis in 35 of those patients in whom the mean pressure was 21.2 ± 1.3 mm. Hg, and in the 21 other patients who had a dominating

stenosis but a certain degree of regurgitation the corresponding mean pressure in the left atrium was 22.9 ± 6.1 mm. Hg.

2. In the remaining 7 patients who had a mitral stenosis in combination with other forms of heart disease or malformations the left atrial pressure varied between 34 and 10 mm. Hg, with a mean pressure of 21.9 mm. Hg.

3. In all 56 patients having a mitral lesion a positive diastolic pressure gradient between the left atrium and the left ventricle was observed. This pressure gradient varied between 36 and 1 mm. Hg, with a mean value of 10.5 ± 0.9 mm. Hg. In 9 patients this pressure gradient was less than 5 mm. Hg and was not considered significant, although this pressure gradient was observed on repeated withdrawal curves as the catheter was pulled through the mitral orifice. In the 35 patients having a pure mitral stenosis the pressure gradient averaged 11.2 ± 1.2 mm. Hg, whereas in the 21 other patients with a dominating mitral stenosis and some regurgitation this diastolic pressure gradient between the left atrium and left ventricle was 9.3 ± 2.5 mm. Hg.

4. In the remaining 7 patients who had mitral lesion in combination with other heart disease there was also a positive diastolic pressure gradient between

TABLE II. THE DEGREE OF DIASTOLIC PRESSURE GRADIENT BETWEEN THE LEFT ATRIUM AND THE LEFT VENTRICLE IN 63 CASES OF MITRAL STENOSIS VERIFIED AT SURGERY

DIASTOLIC PRESSURE GRADIENT LA-LV (MM. HG)	PURE MITRAL STENOSIS	DOMINATING MITRAL STENOSIS + REGURGITATION	MITRAL STENOSIS + OTHER LESION	TOTAL
0– 4	5	5	3	13
5– 9	14	7	2	23
10–14	7	6	1	14
15–19	5	1	1	7
20	4	2	–	6
Total	35	21	7	63

TABLE III. MEAN PRESSURE IN LEFT ATRIUM AND THE DIASTOLIC PRESSURE GRADIENT BETWEEN LEFT ATRIUM AND LEFT VENTRICLE IN 63 CASES OF MITRAL STENOSIS VERIFIED AT SURGERY

GROUP	DIAGNOSIS	NUMBER	MEAN PRESSURE IN LEFT ATRIUM (MM. HG)		DIASTOLIC PRESSURE GRADIENT BETWEEN LA AND LV (MM. HG)	
			RANGE	MEAN VALUE	RANGE	MEAN VALUE
I	Pure mitral stenosis	35	37–10	21.2 ± 1.3	36–2	11.2 ± 1.2
II	Dominating mitral stenosis + regurgitation	21	35–6	22.9 ± 6.1	25–1	9.3 ± 2.5
III	Mitral stenosis + other lesion	7	34–10	21.1	15–1	6.4
I + II	Pure mitral lesion with pure or dominating stenosis	56	37–6	21.9 ± 1.1	36–1	10.5 ± 0.9

the left atrium and the left ventricle, varying between 15 and 1 mm. Hg, with a mean value of 6.4 mm. Hg. Three of those patients had values of less than 5 mm. Hg.

5. The pressure gradient may vary in the same patient. At a slower heart rate with a longer diastolic period, a better equalization between the left atrium and the left ventricle is obtained, causing a smaller pressure gradient. This is evident in patients with atrial fibrillation. The calculated values of the pressure gradient in all cases have been made as a mean value on many heart beats. Periods with a high heart rate can therefore not be used for calculation of the pressure gradient. In such cases it may be impossible to find a representative end-diastolic pressure in the left ventricle.

6. No correlation between the diastolic pressure gradient between the left atrium and the left ventricle and the surgeon's approximative calculation of the size of the orifice could be found.

7. There was some correlation (r = 0.65) between the diastolic pressure gradient between the left atrium and the left ventricle in rest and the minute volume in the 14 patients in whom it was possible to estimate the flow during the pressure measurement (P 0.02 – 0.01).

8. There was no correlation between the pressure gradient and the heart volume or between the pressure gradient and the patient's physical working capacity, as measured on a bicycle ergometer according to Sjöstrand-Wahlund.

DISCUSSION

The damping effect in the system between the heart and the pressure receptors represents a significant course of failure in this investigation. The damping effect in each catheter ought to be checked after each investigation. The damping effect can be studied by introducing small gas bubbles into the pressure receptor or by rotating the catheter along its long axis. Then the pressure gradient obtained will decrease. The mean pressure, on the other hand, will remain, but the amplitude will decrease and the pressure gradient too. The values of the diastolic pressure gradient between the left atrium and the left ventricle that we have found must therefore represent minimal values, whereas the real pressure gradient is much larger. The method is therefore not suitable for a close study of the variations in pressure at the mitral orifice.

Because of the risks involved in this type of investigation no normal subjects have been investigated. On the other hand, we have made corresponding measurements of the pressure gradient in 7 patients with aortic valvular lesions but with normal mitral valves. In those 7 patients there was no pressure gradient. In 3 of those patients the pressure curves were not perfect because of damping. In another instance, a withdrawal curve from the left ventricle to the left atrium was obtained at the time of operation with an open thorax in a patient with pure mitral insufficiency. In this case no pressure gradient could be obtained in spite of the fact that the left atrium was very large.

In this material there is no significant difference between the left ventricular pressure values of patients with a pure mitral stenosis and those of patients

having a concomitant regurgitation in the mitral orifice. Furthermore, there is no significant difference in the diastolic pressure gradient values between patients with pure mitral stenosis and patients with concomitant mitral regurgitation.

CONCLUSIONS

The method outlined is not ideal, since only minimal values can be obtained because of damping effects. But we have found that of 56 patients with a mitral lesion with dominating stenosis, 46 had a positive diastolic pressure gradient of 5 mm. Hg or more between the left atrium and the left ventricle. The other 10 patients had a pressure gradient of between 4 and 1 mm. Hg between the left atrium and the left ventricle, but we have not considered this as a significant gradient. Since no diastolic pressure gradient was observed in any of the 7 control patients who had aortic lesions but healthy mitral leaflets, it seems probable that an end-diastolic pressure gradient over the mitral ostium of at least 5 mm. Hg is necessary to favor the diagnosis of a mitral stenosis.

SUMMARY

1. The end-diastolic pressure gradient between the left atrium and the left ventricle has been determined at rest in 63 patients with mitral valvular lesion. The diagnosis was verified at surgery in all cases.

2. In all patients with a mitral stenosis, there was a positive end-diastolic pressure gradient between the left atrium and the left ventricle, varying between 36 and 1 mm. Hg. In 56 of these patients who had mitral lesions with a dominating mitral stenosis the pressure gradient averaged 10.5 mm. Hg. In 10 patients it was less than 5 mm. Hg. A corresponding pressure gradient could not be observed in 7 patients who had an aortic lesion without a mitral lesion.

3. In 14 patients in whom the minute volume was determined during the measurement of the pressure gradient, there was a slight but probably significant correlation between these two factors.

4. No correlation could be observed between the degree of the pressure gradient and the size of the orifice as measured by the surgeon's observations. Furthermore, in this material no correlation could be found between the pressure gradient and the heart volume or the patient's working capacity.

5. A diastolic pressure gradient over the mitral orifice of at least 5 mm. Hg will indicate the presence of a stenotic component in the mitral valves. However, such a pressure gradient does not help to distinguish cases of pure mitral stenosis from those with a concomitant mitral regurgitation, nor to evaluate the degree of such mitral regurgitation.

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Treatment of Cardiac Arrhythmias With Salts of Ethylenediamine Tetraacetic Acid (EDTA)

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An elevated concentration of calcium ion is known to increase the irritability of the ventricular myocardium of rats,[1,9] dogs,[2,3] and rabbits.[4-6] Conversely, perfusion with calcium-free solution restores sinus rhythm to a rabbit heart with ventricular fibrillation.[7] To determine whether a decreased concentration of calcium was effective in treating human cardiac arrhythmias, salts of ethylenediamine tetraacetic acid were used to lower the concentration of calcium ion in plasma. These salts have been used for chelation of calcium in man since 1950,[8] and doses of 50 mg./Kg. per day have been found to be safe. The results reported in this paper suggest that lowering the amount of calcium in the blood can suppress ectopic beats in some patients.

MATERIAL AND METHODS

A total of 88 intravenous infusions were given to 55 patients. Cardiac arrhythmias were present in 46. The group included 27 men and 19 women. Their ages ranged from 14 to 94 years (average age, 73). Forty-one had heart diseases of varying severity: 23 arteriosclerotic, 10 hypertensive, 3 rheumatic, 2 senile degenerative, 1 syphilitic, 1 myxedematous, and 1 questionable neoplastic heart disease. Five patients had no evidence of heart disease. There were 12 cases of atrial fibrillation, 8 of atrial flutter, 14 of atrial premature beats, 25 of ventricular premature beats, and 1 of ventricular tachycardia. Several patients had two types of arrhythmias at the same time. In patients selected for the study the arrhythmia had been present for at least 48 hours prior to study. A careful clinical study was made of each patient, with particular attention to digitalis medication. Patients who were moribund, had renal insufficiency, hyperpotassemia, or hypocalcemia were not used. A total of 200 to 400 consecutive electrocardiographic complexes were inspected prior to each study, and only those patients were used in whom 8 per cent or more of the complexes stemmed from the same ectopic pacemaker.

The average dose of disodium ethylenediamine tetraacetic acid (Na_2EDTA) was 2.8 (0.5 to 4.0) Gm. It was infused as a 10 per cent solution in physiologic saline. The average time of the

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This investigation was supported by a grant-in-aid from the American Heart Association, and by United States Public Health Service Grant H-3420.

Received for publication June 19, 1959.

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infusion was 17 (8 to 40) minutes, and in most instances was given at a rate of 0.2 Gm. per minute. Dipotassium ethylenediamine tetraacetic acid (K_2EDTA) was administered as a nearly isotonic solution containing 10 Gm. K_2EDTA, 3 Gm. KCl, and 3 Gm. NaCl per liter of water. This solution contained 1 mEq. of potassium per 10 ml. The pH of the Na_2EDTA and K_2EDTA solutions was adjusted to 7.4 before sterilizing. The average dose of K_2EDTA* was 1.9 (1.3 to 3.0) Gm., given over an average of 23 (10 to 33) minutes. Patients received about 0.1 Gm. of K_2EDTA and 1 mEq. of potassium per minute. When potassium chloride solution was given alone, the solution contained 10 mEq. of potassium per 100 ml. of 0.45 per cent saline. Patients received about 1 mEq. of potassium per minute; the average dose was 17 (8 to 24) mEq., given in an average of 20 (8 to 45) minutes.

All infusions were made under constant electrocardiographic observation. In many patients the heart sounds were also recorded, by means of a previously described technique.[17] In 5 patients the brachial artery pressure was recorded through an indwelling Riley needle by means of a Statham strain gauge, and in 4 patients the right ventricular and pulmonary artery pressures were recorded during routine right heart catheterization. The infusion of Na_2EDTA was stopped when the arrhythmia was abolished, or the dose exceeded 3 to 4 Gm., or the symptoms of hypocalcemia appeared. Infusion of K_2EDTA was terminated for the above-mentioned reasons, and also when electrocardiographic signs of potassium toxicity appeared. Following the infusion of Na_2EDTA and K_2EDTA, most patients were given 5 to 10 ml. of 10 per cent calcium chloride intravenously, and the effects were observed on the electrocardiogram and heart sound tracing.

Serum concentrations of calcium, sodium, and potassium were determined in each patient before and immediately after infusion. Blood pH was determined in 11 patients. Calcium was determined by the method of Clark and Collip.[16] It was shown that within the limits of experimental error this method did not determine the calcium chelated with EDTA.[30] Potassium and sodium were determined with a flame photometer, using lithium as an internal standard.

RESULTS

I. *Na_2EDTA.—*

Serum electrolytes: Only the calcium concentration showed consistent changes. It decreased from 4.75 (3.8 to 5.7) mEq./L. before infusion to 3.55 (2.6 to 4.6) mEq./L. after infusion. The decrease ranged from 0.7 to 2.0 mEq./L. Sodium concentration was 141 (126 to 152) mEq./L. Potassium concentration was 4.2 (3.9 to 5.2) mEq./L., and pH was 7.42 (7.35 to 7.52).

Effect on blood pressure: Systolic and diastolic blood pressures by both indirect and direct methods were usually 5 to 20 mm. Hg lower after the infusion. The ascending limb of the brachial artery pressure curve was prolonged. This prolongation seemed to parallel the prolongation of the S-T segment. In one patient an anacrotic notch appeared typical of that seen in patients with aortic valvular stenosis (Fig. 1). The pulmonary arterial and right ventricular pressure records were difficult to evaluate because of changes in heart rate, and the slight fall in pressure usually seen after the infusion of Na_2EDTA. However, the ascending limb did appear to undergo a decrease in slope similar to that in the brachial artery (Fig. 2).

Electrocardiogram and duration of mechanical systole: In 75 per cent of the patients the R-R interval decreased after the infusion of Na_2EDTA. This averaged 0.103 (0.03 to 0.25) second. Q-oT, Q-aT, Q-T, and Q-2nd sound[17] (Q-2s), corrected for heart rate, were all lengthened by 10 to 40 per cent. A detailed study of these intervals will be reported separately.[18] Although all the above-

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*The use of K_2EDTA required caution because of the well-known potentiation of cardiotoxicity of potassium by hypercalcemia.[15] A safe dose was established by us after preliminary trials in dogs.

mentioned intervals were prolonged, the greatest increase occurred in the Q-oT_c interval. This was due to a prolongation of the S-T segment without any definite changes in the duration of the T wave. Prolongation of mechanical systole did not always equal the prolongation of the Q-T interval. In more than half of the patients the lengthening of the Q-T interval exceeded that of the Q-2s interval.

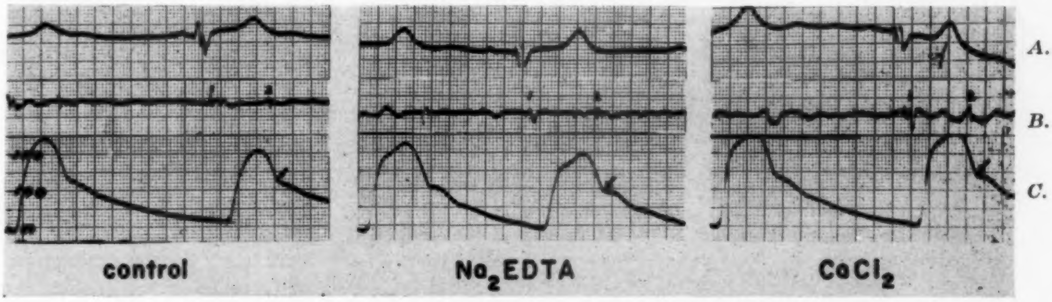

Fig. 1.—Lead II of the electrocardiogram (*A*), phonocardiogram (*B*), and pressure tracing from brachial artery (*C*) of an 80-year-old man with mild cardiomegaly but no evidence of valvular heart disease. The first and second heart sounds are marked *1* and *2*. The arrow points at the incisura of the brachial arterial pressure tracing. Control: R-R, 1.16; Q-aT, 0.33; Q-T, 0.45; Q-incisura, 0.47; and Q-2s, 0.42 sec. Brachial arterial pressure, 165/55 mm. Hg. Ca_s, 4.6; K_s, 4.3; Na_s, 146 mEq./L.; pH, 7.50. After the administration of 3.0 Gm. of Na_2EDTA in 28 minutes: Ca_s, 3.0 mEq./L.; R-R, 0.96; Q-aT, 0.37; Q-T, 0.48; Q-incisura, 0.50; and Q-2s, 0.46 sec. Brachial arterial pressure, 160/45 mm. Hg. Immediately after the administration of 9 ml. of 10 per cent $CaCl_2$ solution: R-R, 1.10; Q-aT, 0.33; Q-T, 0.40; Q-incisura, 0.47; and Q-2s, 0.43 sec. Brachial arterial pressure, 180/50 mm. Hg. Note the anacrotic notch after Na_2EDTA.

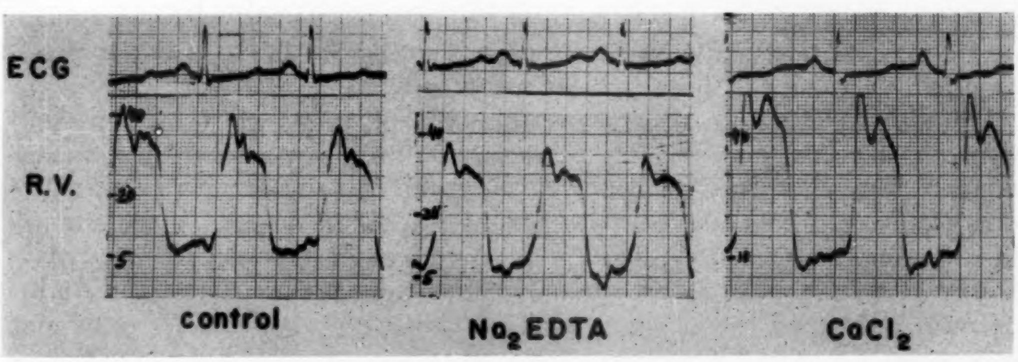

Fig. 2.—Electrocardiogram and right ventricular pressure (*R.V.*) of a 14-year-old girl with kyphoscoliosis. After the administration of 2.5 Gm. of Na_2EDTA in 25 minutes: Ca_s decreased from 4.9 to 4.0 mEq./L. Note the prolonged Q-T interval and the slow ascent of the right ventricular pressure curve. After administration of 5 ml. of 10 per cent $CaCl_2$ solution the Q-T interval is shorter, and the ascent of the right ventricular pressure curve steeper.

In the remaining patients, the prolongation of Q-T and Q-2s was equal, except in one case in which mechanical systole exceeded the Q-T interval. Other electrocardiographic changes included lengthening of the P-R interval in 3 cases, and shortening in one case, frequent changes in the shape and polarity of the T wave, and a decreased amplitude of the U wave.

Atrial fibrillation and flutter: In none of the 9 patients with atrial fibrillation was the rhythm changed by the infusion of Na_2EDTA. In one of 5 patients with atrial flutter a sinus rhythm was established and maintained for the following 2 weeks of observation. All those with flutter were receiving digitalis, and in 3 of them, quinidine had been used without success. Na_2EDTA failed to change the rate of flutter, but in one patient the A-V block changed from 2:1 to 4:1.

TABLE I. EFFECT OF Na_2EDTA ON VPC AND APC

	DIGITALIS		NO DIGITALIS		TOTAL
	SUCCESS (NUMBER OF PATIENTS)	FAILURE (NUMBER OF PATIENTS)	SUCCESS (NUMBER OF PATIENTS)	FAILURE (NUMBER OF PATIENTS)	
VPC	5	4	11	5	25
APC	2	2	5	5	14
Total	7	6	16	10	39

Atrial and ventricular premature contractions: A therapeutic success was designated if ectopic beats were abolished or significantly decreased. A significant decrease was arbitrarily defined as a change from 50 per cent or more ectopic beats to 25 per cent or less, a change from 30-49 per cent to 15 per cent or less, and a change from 8-29 per cent to 2 per cent or less. A failure consisted of an insignificant decrease, lack of change, or an increase in the percentage of ectopic beats. Of 14 patients with atrial permature beats (APC), 7 had a therapeutic success. Of 25 patients with ventricular premature beats (VPC), successes occurred in 16; in 10 of these, all VPC were abolished.

In the patients with APC the percentage of success was the same in patients receiving digitalis as in those who were not. In patients with VPC, success occurred somewhat more frequently in the group of patients not receiving digitalis (Table I). Examples of the action of Na_2EDTA on ectopic beats are illustrated in Figs. 3 and 4. There was no correlation between the severity of the heart disease and the response of ectopic beats to Na_2EDTA. The mean decrease (1.12 mEq./L.) of serum calcium in patients whose ectopic beats were suppressed was nearly identical with the mean decrease (1.17 mEq./L.) in those whose ectopic beats were not suppressed.

In the patient with ventricular tachycardia, Na_2EDTA failed to change the rhythm. Quinidine and procaine amide had also failed to abolish this.

Side effects: Several patients complained of pain along the course of the vein receiving the infusion. This was usually relieved by warming the solution to body temperature and by hot packs or gentle massage of the arm. In 4 patients it was necessary to slow the rate of the infusion. Single instances of circumoral numbness, paresthesia of the extremities, nausea, a feeling of warmth in the face, dizziness, vomiting, and severe apprehension occurred. With their occurrence, the infusion was stopped.

Calcium chloride after infusing Na_2EDTA: Calcium chloride abolished the alterations in the electrocardiogram caused by Na_2EDTA. The heart rate slowed and Q-oT, Q-aT, Q-T, and Q-2s intervals shortened, usually becoming shorter than the control values. The injection of calcium chloride was followed by a reappearance of ectopic beats in 6 of 9 patients whose VPC had disappeared after the infusion of Na_2EDTA, and in 3 of 4 patients whose APC had been abolished by Na_2EDTA.

Comment.—We were unable to discover any obvious differences between patients whose ectopic beats were suppressed and those whose ectopic beats were unaffected by Na_2EDTA. Analysis of electrocardiograms revealed that in the majority of the patients with ventricular ectopic beats the coupling interval

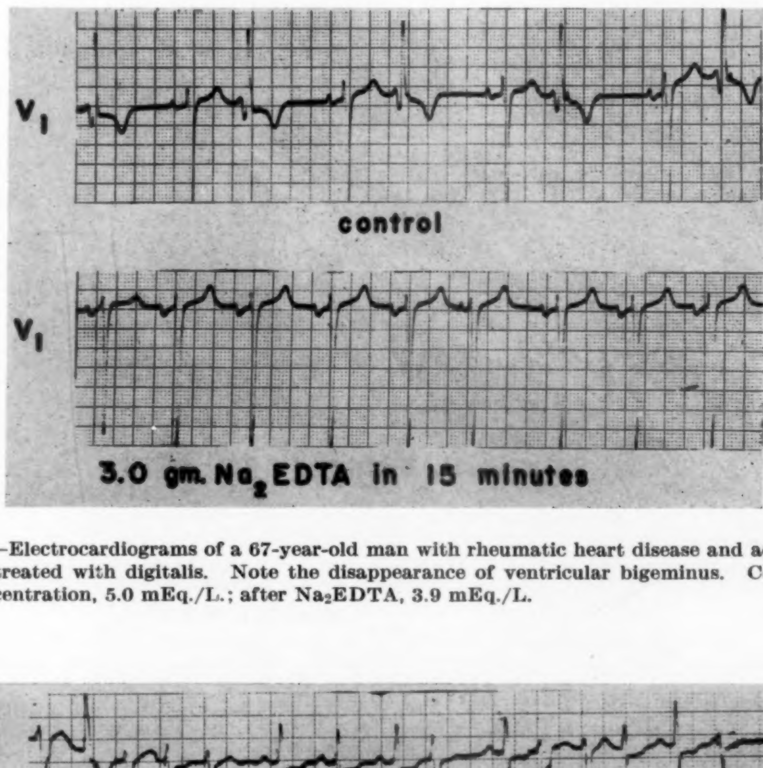

Fig. 3.—Electrocardiograms of a 67-year-old man with rheumatic heart disease and aortic regurgitation, not treated with digitalis. Note the disappearance of ventricular bigeminus. Control serum calcium concentration, 5.0 mEq./L.; after Na_2EDTA, 3.9 mEq./L.

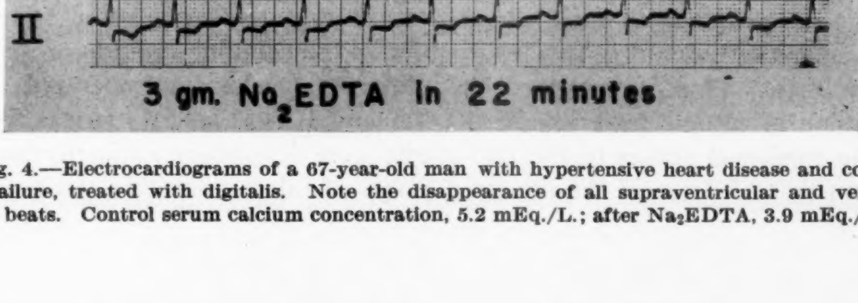

Fig. 4.—Electrocardiograms of a 67-year-old man with hypertensive heart disease and congestive heart failure, treated with digitalis. Note the disappearance of all supraventricular and ventricular ectopic beats. Control serum calcium concentration, 5.2 mEq./L.; after Na_2EDTA, 3.9 mEq./L.

of these beats became longer during and after the infusion of Na_2EDTA. Hypocalcemia caused a progressive lengthening of the S-T segment and movement of the apex of the T wave to the right, with a resulting prolongation of the Q-T interval. The increased duration of electrical systole was apparently accompanied by an increased duration of the refractory period of the ventricular myocardium. As a rule, ventricular premature beats appear after the inscription of the apex of the T wave after the infusion of Na_2EDTA. Ventricular premature beats showed the same time relation to the apex of the T wave as before the infusion, but the absolute duration of the coupling interval necessarily became longer[19] (Fig. 5). This increase in duration of systole and the myocardial refractory phase might be responsible for the suppression of ectopic beats. Another consideration was the increase in heart rate after the infusion of Na_2EDTA.

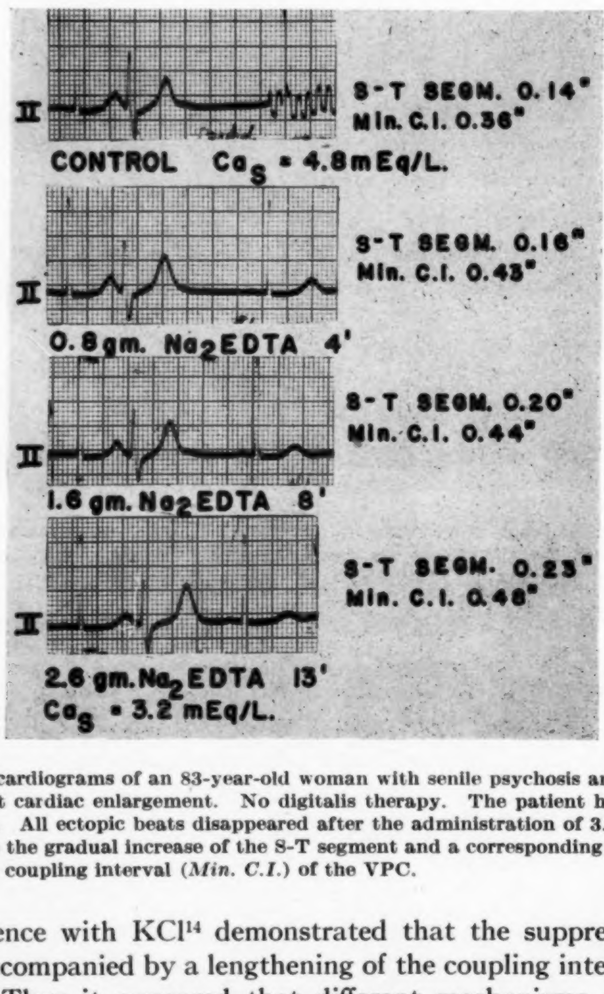

Fig. 5.—Electrocardiograms of an 83-year-old woman with senile psychosis and mild hypertensive heart disease without cardiac enlargement. No digitalis therapy. The patient had 30 per cent VPC and 3 per cent APC. All ectopic beats disappeared after the administration of 3.0 Gm. of Na_2EDTA in 15 minutes. Note the gradual increase of the S-T segment and a corresponding increase in the duration of the minimum coupling interval (*Min. C.I.*) of the VPC.

Previous experience with KCl[14] demonstrated that the suppression of ectopic beats was not accompanied by a lengthening of the coupling interval or a change in heart rate. Thus it appeared that different mechanisms operated during suppression of ectopic beats by Na_2EDTA and KCl (Fig. 6). It was thought that the combined action of the two might have a stronger antiarrhythmic effect than that of either of the two used alone. To determine this, patients were

selected whose ectopic beats had not been suppressed by Na_2EDTA or KCl given separately; patients with atrial fibrillation and flutter were also used, because these arrhythmias had been found to be resistant to either KCl or Na_2EDTA.

II. *Na_2EDTA and KCl.*—Infusion of Na_2EDTA was followed immediately by an infusion of KCl in 10 patients. During the infusion of KCl, the calcium concentration, which had been decreased by Na_2EDTA, increased an average of 0.35 mEq./L. Serum potassium levels increased an average of 0.5 (0.1 to 1.0) mEq./L. In 5 patients with atrial fibrillation and in one with atrial flutter the administration of KCl after Na_2EDTA failed to change the rhythm. In 2 of the 4 patients with ectopic beats the administration of KCl after Na_2EDTA appeared to be more effective than either given alone. No untoward effects were noted during the administration of KCl after Na_2EDTA. Electrocardiograms frequently showed peaking of the T waves characteristic of hyperpotassemia.

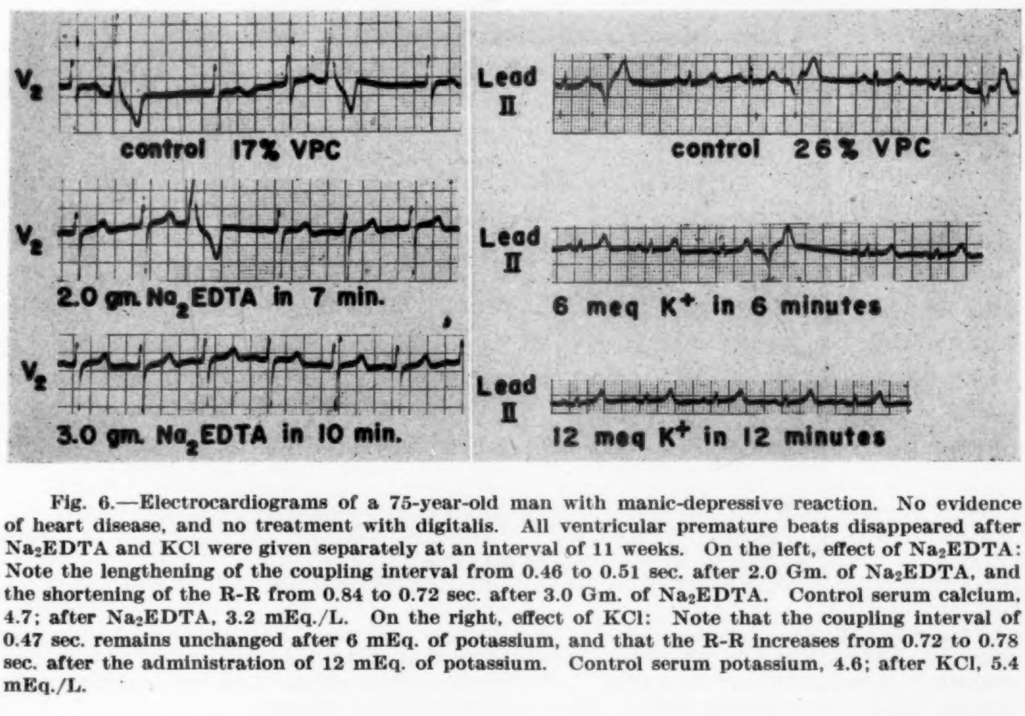

Fig. 6.—Electrocardiograms of a 75-year-old man with manic-depressive reaction. No evidence of heart disease, and no treatment with digitalis. All ventricular premature beats disappeared after Na_2EDTA and KCl were given separately at an interval of 11 weeks. On the left, effect of Na_2EDTA: Note the lengthening of the coupling interval from 0.46 to 0.51 sec. after 2.0 Gm. of Na_2EDTA, and the shortening of the R-R from 0.84 to 0.72 sec. after 3.0 Gm. of Na_2EDTA. Control serum calcium, 4.7; after Na_2EDTA, 3.2 mEq./L. On the right, effect of KCl: Note that the coupling interval of 0.47 sec. remains unchanged after 6 mEq. of potassium, and that the R-R increases from 0.72 to 0.78 sec. after the administration of 12 mEq. of potassium. Control serum potassium, 4.6; after KCl, 5.4 mEq./L.

Comment.—In a small group of patients with cardiac arrhythmias the administration of KCl after Na_2EDTA failed to show dramatic results. In certain cases the combination seemed to have a stronger antiarrhythmic action than did the use of either separately. In order to obviate the rapid increase in the concentration of calcium which occurred during the administration of KCl, the effect of K_2EDTA was studied.

III. *K_2EDTA.*—In 11 patients receiving K_2EDTA the concentration of serum potassium increased by 0.72 (0.1 to 1.0) mEq./L., whereas serum calcium

decreased by 0.8 (0.4 to 2.1) mEq./L. The highest concentration of serum potassium after infusion was 6.5 mEq./L., and the lowest serum calcium was 2.8 mEq./L. Pain along the vein was more pronounced with K_2EDTA than with Na_2EDTA, and necessitated a slowing of the infusion rate in 3 patients. The electrocardiograms showed features characteristic of hypocalcemia and hyperpotassemia. Widening of the QRS complex was not observed. The infusion was discontinued when peaking of the T wave became pronounced.

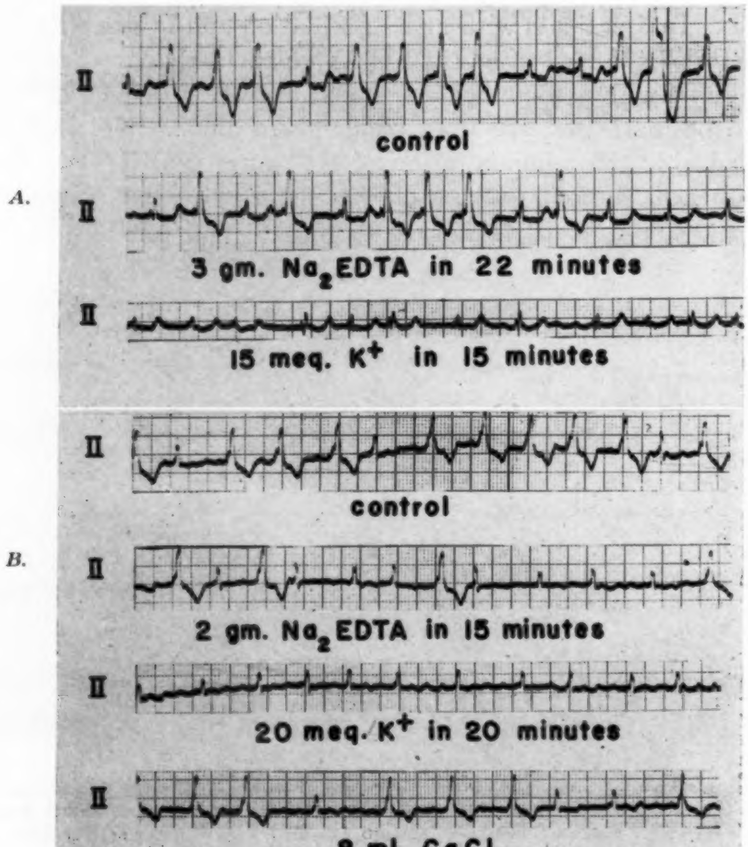

Fig. 7.—*A*, Electrocardiograms of an 85-year-old male schizophrenic patient with arteriosclerotic heart disease. See text. *B*, Electrocardiograms of an 83-year-old male patient with chronic brain syndrome. Administration of Na_2EDTA, KCl, and $CaCl_2$ consecutively. Note the reappearance of aberrant ventricular conduction after the administration of $CaCl_2$. See text.

Atrial fibrillation was present in 6 patients and remained unaffected. Atrial flutter was present in 3 patients and also remained unchanged. However, the rate of flutter slowed from 400 to 300 per minute in one case, and from 300 to 240 per minute in another case. One patient with atrial and ventricular ectopic beats who had showed no response when Na_2EDTA and KCl were administered alone, also failed to respond to K_2EDTA. In one patient with atrial fibrillation, ventricular premature beats appeared during infusion of K_2EDTA.

Comment.—The administration of K_2EDTA to a small group of patients failed to show an antiarrhythmic action superior to KCl or Na_2EDTA given alone. Two instances of slowing of atrial flutter were observed. Such slowing was not observed with either Na_2EDTA or KCl.

IV. *The Effects of Na_2EDTA and K_2EDTA on Intraventricular Conduction Disturbances.*—During the administration of Na_2EDTA to 2 patients with atrial fibrillation an intraventricular conduction disturbance was noted to improve. In one of these patients who was receiving digitalis, 39 per cent of the ventricular complexes showed aberrant conduction of a right bundle branch block type. These complexes disappeared after infusion of Na_2EDTA. In another patient not receiving digitalis, 87 per cent of the ventricular complexes showed a left bundle branch block type of aberration. After infusion of Na_2EDTA the number of aberrant complexes decreased to 38 per cent. When this was followed by the administration of 7 mEq. of KCl, all aberrant complexes disappeared (Fig. 7,*A*). Subsequently, another patient with a left bundle branch block type of aberration who was receiving digitalis was studied. Na_2EDTA did not change the aberration, whereas KCl alone, KCl after Na_2EDTA, and K_2EDTA abolished it (Fig. 7,*B*).

DISCUSSION

The results of animal experiments dealing with myocardial irritability during hypocalcemia have not yielded conclusive results.[7] A low concentration of calcium protected hypothermic dogs[2] and isolated rabbit hearts[6] from ventricular fibrillation. Other experiments with isolated rabbit hearts showed an increased incidence of ventricular fibrillation when the normal concentration of calcium in the perfusing solution was reduced to one half, one quarter, or one eighth, but no ventricular fibrillation occurred when the heart was perfused with a calcium-free solution.[5] Similar observations were made on the isolated atria of rabbits.[21] Lowering the serum calcium in anesthetized rabbits was occasionally associated with the appearance of atrial premature contractions and ventricular fibrillation.[32]

Disappearance of ectopic beats after infusion of Na_2EDTA may be attributed to induced hypocalcemia (EDTA, in the physiologic pH range, combines preferentially with calcium rather than magnesium[8]), or to a direct effect of EDTA on the myocardium. Other factors to be considered are: lying quietly during the infusion, a fall in blood pressure, and an increase of heart rate. In one patient the number of ectopic beats decreased after a change from recumbent to upright position, and also mild exercise. However, in several other patients in whom Na_2EDTA suppressed ectopic beats the increased heart rate prior to infusion had no effect on the arrhythmia. The success or failure to abolish ectopic beats was generally not related to the change in heart rate.

A direct action of EDTA on the myocardium has been reported.[20] If such an action were present, it seems unlikely that it could have abolished the ectopic beats, because in many patients the ectopic beats reappeared promptly after intravenous administration of calcium chloride. Our observations favor the assumption that induced hypocalcemia was responsible for suppression of ectopic beats.

Arrhythmias produced by toxic doses of digitalis in dogs could be abolished by the administration of Na_2EDTA[26] or K_2EDTA.[27] In analogy to the animal experiments, the disappearance of ectopic beats in patients receiving digitalis after the administration of Na_2EDTA was attributed to a decrease in the toxic action of digitalis by chelation of serum calcium.[28,29] The synergistic action of calcium and digitalis on contractility is well known.[22,23] The action of a high concentration of calcium[24] and of digitalis glycosides[25] on the shape of the ventricular action potential is similar. However, in our experience, induced hypocalcemia also abolished ectopic beats in patients not receiving digitalis. Hence, the usefulness of Na_2EDTA for diagnosing digitalis overdosage appears to be limited.

The effects of Na_2EDTA on the shape of human electrocardiograms have been described previously.[31] These electrocardiographic effects and the effect on the duration of mechanical systole can probably be attributed solely to the decreased level of ionized calcium.

Our observations of the longer coupling intervals of ventricular ectopic beats strongly suggests a prolongation of the refractory period in the ventricular myocardium. It is tempting to attribute the antiarrhythmic action of induced hypocalcemia to this phenomenon.

Whether the administration of Na_2EDTA will find a wide clinical application in the management of cardiac arrhythmias cannot be definitely answered on the basis of this study. In our experience, Na_2EDTA was usually not superior to other antiarrhythmic agents. The necessity of using fairly large amounts of fluids intravenously, the time consumed in monitoring the electrocardiograms, and the occasional unpleasant side effects[29,31] seem to limit a wide clinical applicability of Na_2EDTA for suppression of cardiac arrhythmias. The usefulness of Na_2EDTA with KCl or of K_2EDTA has not been definitely established, and further observations are necessary. The fact that the rate of atrial flutter was slowed on two occasions offers some promise of possible therapeutic effectiveness of K_2EDTA in this type of arrhythmia.

SUMMARY

1. An average of 2.8 (0.5 to 4.0) Gm. of Na_2EDTA was given intravenously to 46 patients with cardiac arrhythmias. The side effects were minor. The concentration of serum calcium decreased on an average of 1.18 mEq./L. Atrial ectopic beats were abolished or significantly suppressed in 7 out of 14 patients, and ventricular ectopic beats were suppressed in 16 out of 25 patients. In 9 instances of atrial fibrillation and 4 of atrial flutter, Na_2EDTA was ineffective. Atrial flutter was abolished in one patient.

2. Na_2EDTA was about equally effective in suppressing ectopic beats in patients not receiving digitalis as in those receiving it. There was no difference in the effect of Na_2EDTA in patients without heart disease and in those with varying degrees of heart disease. The success or failure was not related to changes in heart rate or degree of induced hypocalcemia.

3. The suppression of ectopic beats after infusion of Na_2EDTA was attributed to the induced hypocalcemia, because in the majority of patients in

whom calcium chloride was given after termination of the infusion of Na_2EDTA, the ectopic beats reappeared.

4. The main effect of induced hypocalcemia on the electrocardiogram consisted of prolongation of the S-T segment and of the coupling interval of the premature beats. The latter was attributed to lengthening of the refractory phase of the ventricular myocardium, which was considered as a possible mechanism of the action of Na_2EDTA on ectopic beats.

5. Intravenous infusion of KCl followed infusion of Na_2EDTA in 10 patients. In addition, 11 patients received an intravenous infusion of 1.3 to 3.0 Gm. of K_2EDTA. The combined administration of chelating agent and potassium appeared to have a stronger antiarrhythmic action than did the infusion of either substance alone in only a very few cases.

We wish to express our gratitude to Dr. Rupert Chittick, Superintendent of Vermont State Hospital, Waterbury, Vt., for his kind permission to study the patients at that institution; to Dr. A. Carpenter, Dr. A. Bickford, Dr. B. Tabakin, and Dr. R. Bouchard for help with certain experiments; to Miss B. Bolton for technical help; and to Dr. W. van B. Robertson and Dr. E. Lepeschkin for advice and help in preparation of the manuscript.

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The Clinical Contribution of Electrocardiography in Mechanical Malformations of the Cardiovascular System

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The principal contribution of the electrocardiogram in the study of patients with congenital cardiovascular malformations (most commonly mechanical defects with an otherwise normal myocardium) is the evidence it provides of single-chamber functional "strain" and anatomic "enlargement." Now it is usually considered that a cardiovascular examination is incomplete if any of the "standard," and perhaps some of the not so standard, technical diagnostic methods, such as electrocardiography, fluoroscopy and conventional radiography, cardiac catheterization, and contrast angiocardiography, are omitted. It is usually considered, further, that the maximum value of any one procedure is somehow or other enhanced by correlation with the specific contributions of the others. The rationale for this comprehensive approach is probably valid, and most applicable clinically, particularly in the investigative phase of study in which the precise values and limitations of each procedure are not adequately known. As these become more accurately defined, it must be realized that each of the various diagnostic techniques have an intrinsic and specific contribution which is, or should be, independent of all other techniques, and that the only question then is one of comparison: Which method provides a given type of diagnostic information with the least risk, the greatest technical ease and facility, the maximum accuracy, etc.? Against an extensive correlative background certain somewhat categorical claims may, on the foregoing basis, be made concerning the clinical contribution of the electrocardiogram, beginning with some of its principal advantages over other diagnostic methods, assuming of course the validity of the proposed electrocardiographic correlations.

CLINICAL CONTRIBUTION OF THE ELECTROCARDIOGRAM

Cardiac Catheterization (*with reference to the electrocardiogram as an index of physiologic cardiac chamber work*).—(1) Electrocardiography is a simple, technically easy procedure, which is safe at all ages and under practically all clinical

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From the Division of Pediatric Cardiology, Henry Ford Hospital, Detroit, Mich.
Read in the Symposium on Pediatric Cardiology, before the Joint Meeting of the Section on Diseases of the Chest with the Section on General Practice, June 27, 1958, San Francisco, Calif.
Received for publication April 17, 1959.

circumstances. (2) Cardiac catheterization, particularly in infants and children, only provides physiologic information concerning pressure and flow relations under resting conditions, that is, with basal cardiac output, while the electrocardiogram probably reflects more completely the average work required of the heart under all of the various conditions of daily life. (3) Without simultaneous and accurate determinations of cardiac output, which may be technically difficult especially in infants and young children, intracardiac and intravascular pressures (including transvalvular gradients) and blood oxygen differences (involving the estimation of shunt volumes) are of no *absolute* value in the determination of single-chamber work, and under certain circumstances may even be grossly misleading. Any means, however, such as electrocardiographic, of estimating total individual cardiac chamber work or size would automatically eliminate this particular type of difficulty.

Conventional Radiography (*with reference to the electrocardiogram as an index of individual heart chamber size*).—(1) The sensitivity of the electrocardiogram aids in detecting minimal to even moderate degrees of right or left ventricular hypertrophy prior to the occurrence of any increase in the volume of the chamber concerned. (2) The electrocardiogram is superior in identifying according to anatomic location specific (that is, predominant) right and left ventricular as well as right and left atrial activation which, interpreted in terms of individual chamber work and size, helps to eliminate the nonspecificity which depends radiographically on variations in cardiac position, superimposition of extracardiac structures, changes due to the phase of respiration, etc.

Direct Anatomic Study (*with reference to the electrocardiogram as an index of physiologic work versus anatomic size, again of the individual chambers of the heart*).—(1) Particularly in early infancy, the electrocardiogram may display evidence of increased ventricular work, especially that due to increased pressure, which has not existed over a sufficiently long period of time to result in anatomically demonstrable chamber enlargement, such as muscular hypertrophy in the case of increased pressure-work. (2) It is possible that the electrocardiogram may actually provide a more accurate over-all in vivo picture of individual cardiac chamber volume and myocardial thickness than postmortem measurements, since, in the first place, the latter are post mortem, and, in the second place, there are inherent difficulties in making accurately representative anatomic measurements.

PROPER RECORDING OF THE ELECTROCARDIOGRAM

The next question to be considered is that of what constitutes a properly recorded electrocardiogram from which reliable information regarding cardiac chamber work and size may be extracted. Some of the most important requirements are those noted below.

1. For scalar electrocardiographic leads (and it is believed that these are, for the most part, entirely adequate for the purposes in question) particular emphasis is placed on exploring leads from the precordium, which should be "unipolar," and which should be taken with sufficient care to avoid surface conduction between the various exploring positions.

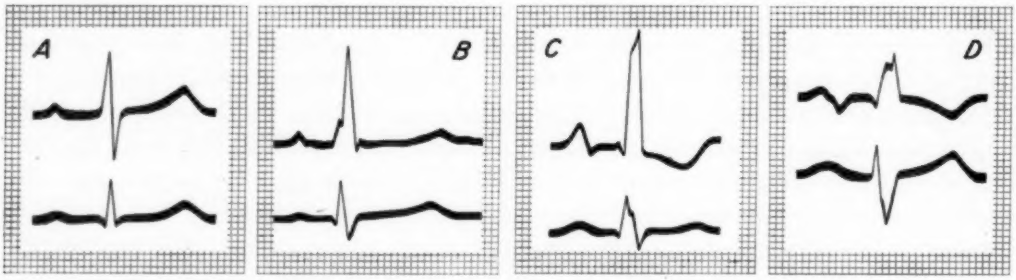
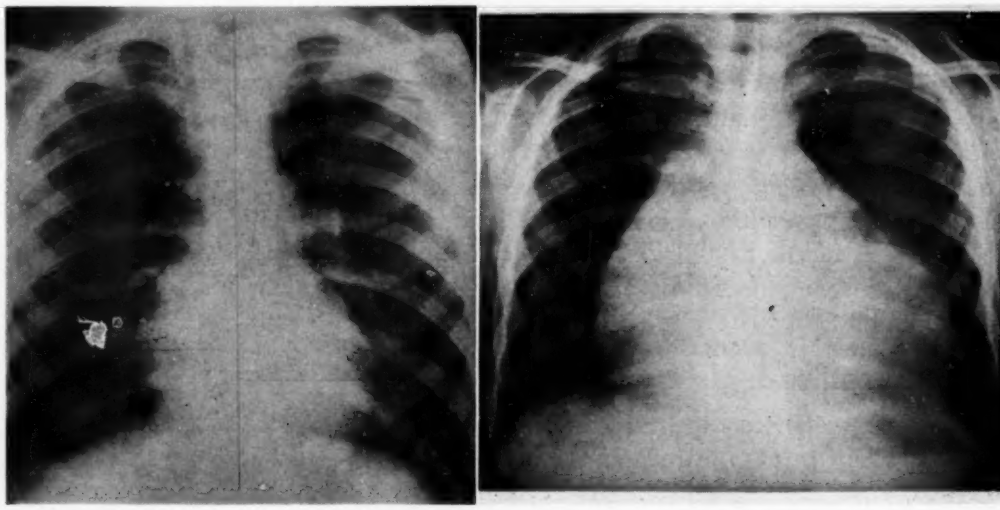


Fig. 1.—Pulmonary stenosis. These four sets of simultaneously recorded precordial leads (V_1 above and V_6 below) represent different typical patterns of progressively increasing degrees of right ventricular hypertension, hypertensive work, and the resulting anatomic enlargement of the right ventricle. The ages of the patients represented are: *A*, 6 years; *B*, 5 years; *C* and *D*, 4 years. In *A*, the only evidence of right ventricular hypertension, and probable hypertrophy, is T-wave positivity in Lead V_1, with a normal amplitude (R = 50 per cent RS) and inscription time of RS in this lead and normal ventricular deflections in leads from the opposite or left side of the precordium (represented here by Lead V_6). In *B*, in addition to T-wave positivity, there is further evidence of right ventricular hypertrophy in the form of increased positive amplitude and delayed inscription time of RS, both in Lead V_1. Both of these sets of precordial leads probably represent uncomplicated right ventricular hypertrophy, that is, without superimposed dilatation and without sufficient increase in chamber volume to be detected with certainty by conventional radiography (Fig. 2,*A*). In *C* and *D*, the electrocardiographic patterns, of almost certainly combined right ventricular enlargement and right bundle branch block, represent marked degrees of combined right ventricular hypertrophy and dilatation, with additional evidence of associated enlargement of the right atrium. Cardiac enlargement is, of course, also obvious in the x-ray, although whether this is entirely right-sided is perhaps not so obvious. From the radiographic evidence of decreased pulmonary vascularity, one can also make the etiologic diagnosis of right ventricular outflow obstruction (pulmonary valvular stenosis or primary pulmonary artery hypertension), which must be further differentiated on the basis of clinical and cardiac catheterization data.



A. *B.*

Fig. 2.—These two posteroanterior roentgenograms correspond to the electrocardiograms in Fig. 1. and both are instances of uncomplicated right ventricular outflow obstruction with right ventricular hypertension and resulting hypertrophy. In *A*, the hypertrophy is probably "concentric," that is, without superimposed dilatation. In *B*, there is almost certainly combined hypertrophy and dilatation, which, as the electrocardiogram indicates, is entirely right-sided.

2. Precordial leads must be included, in addition to the "standard" six positions if necessary, which represent predominant activation derived from probably the full mid-epicardial regions of both the right and the left ventricles. This may necessitate exploring leads from the right hemithorax anteriorly, such as Leads V_{4R} and V_{3R}, and from the left chest posteriorly, such as Leads V_7 and V_8, and occasionally others.

3. Technically, the recording instrument must have at least the accuracy of response of a good string galvanometer. In addition, the following adjuncts are either extremely helpful or absolutely imperative, depending upon the particular point requiring electrocardiographic clarification: (a) the availability of simultaneous leads in order to have some fixed point of reference for the more accurate measurement of inscription times for the various deflections and in order to relate comparable electrical events on either side of the precordium, (b) the availability of a suitable means for electronic amplification with which distortion of wave form may be carefully avoided, and (c) the availability of fast film-paper speed in order to amplify the recorded variations in potential on the time axis.

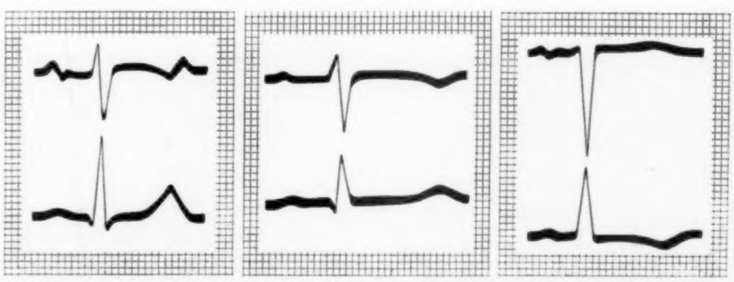
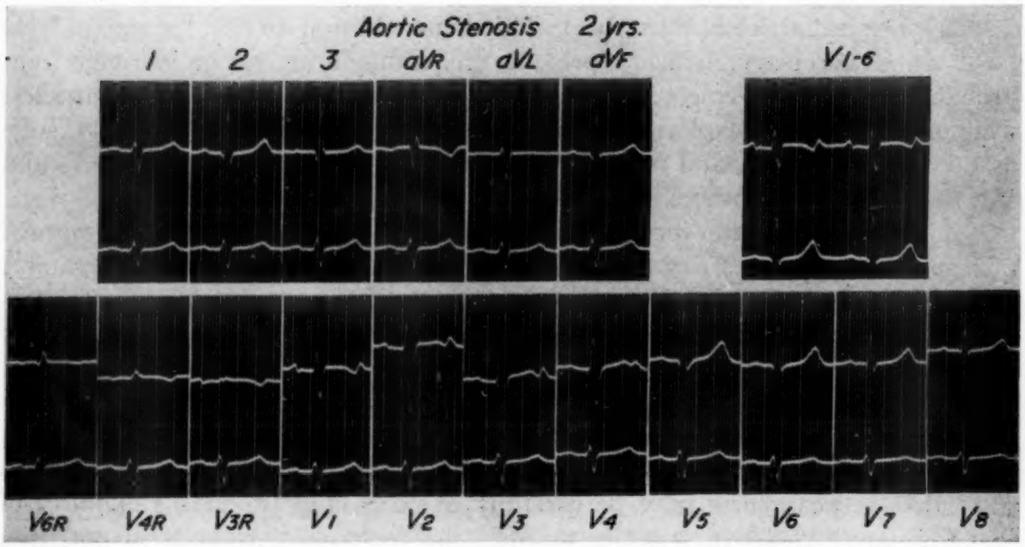
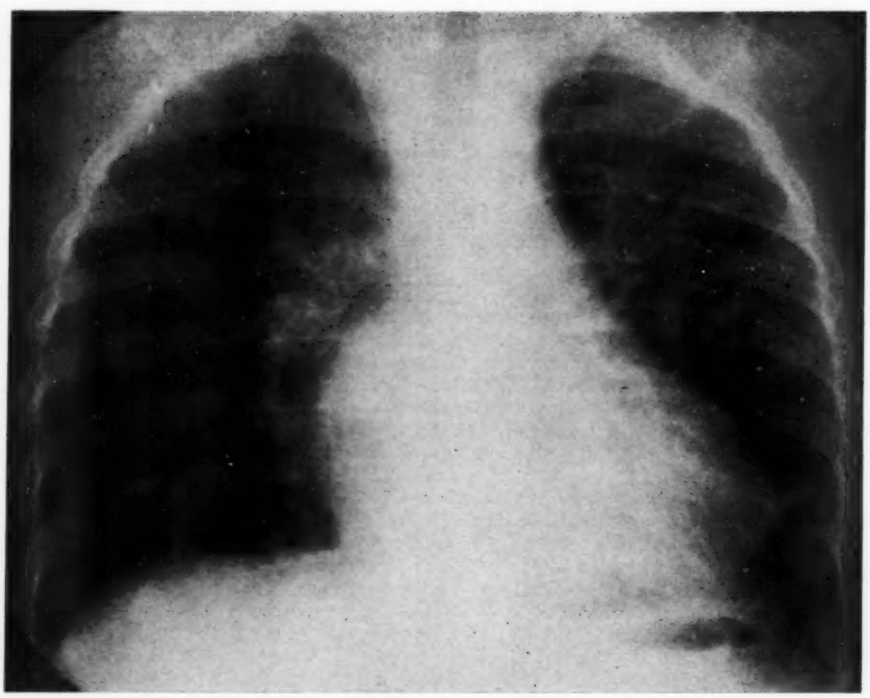


Fig. 3.—Aortic stenosis. These three sets of simultaneously recorded precordial leads (V_1 above and V_6 below) represent different typical patterns of various degrees of left ventricular hypertension, hypertensive work, and the resulting anatomic enlargement of the left ventricle. The ages of the patients represented are: *A*, 2 years; *B* and *C*, 10 years. In *A*, the only electrocardiographic abnormality is an apparently primary increase in the positive amplitude of T in Lead V_6 (primary in the sense that there are no associated changes in QRS to which the T-wave configuration could be secondary). This left precordial lead pattern would appear to be analogous to that observed on the opposite side in uncomplicated right ventricular hypertension (Fig. 1,*A*). Left ventricular hypertension (200/0-8 mm. Hg) was demonstrated by retrograde aortic catheterization. The complete electrocardiogram and posteroanterior roentgenogram of this patient are shown in Fig. 4. In *B*, in which case left ventricular hypertension (170/0-10 mm. Hg) was also demonstrated by retrograde aortic catheterization, the T waves in Lead V_6 are still positive but with what appears to be approaching a —+ configuration. This T-wave pattern becomes even more pronounced in leads farther to the left (V_7 and V_8), as shown in the complete record in Fig. 5. Additional evidence of left ventricular hypertrophy consists of a delayed inscription time of the RS deflection (0.04 sec.) in leads from the left side of the precordium, probably with some resulting increase in the positive area inscribed under QRS in these leads. This type of precordial lead pattern appears to be compatible with uncomplicated left ventricular hypertension and hypertrophy, that is, without any significant degree of superimposed dilatation, and is therefore difficult if not impossible to detect by conventional radiographic techniques (Fig. 5). In *C*, there is gross left precordial lead T-wave inversion, which may be an expression of (1) secondary effect of an increased positive area inscribed under QRS, (2) left ventricular dilatation superimposed on a marked degree of hypertrophy, (3) a relative if not absolute decrease in coronary artery blood flow due to the dynamic effect of the aortic valvular obstruction (aortic hypotension and left ventricular hypertension). This degree of left ventricular enlargement is, of course, usually very much apparent radiographically (Fig. 6). Note the absence of electrocardiographic evidence of left atrial enlargement even with the most advanced degree of left ventricular hypertrophy and dilatation of this hemodynamic type.

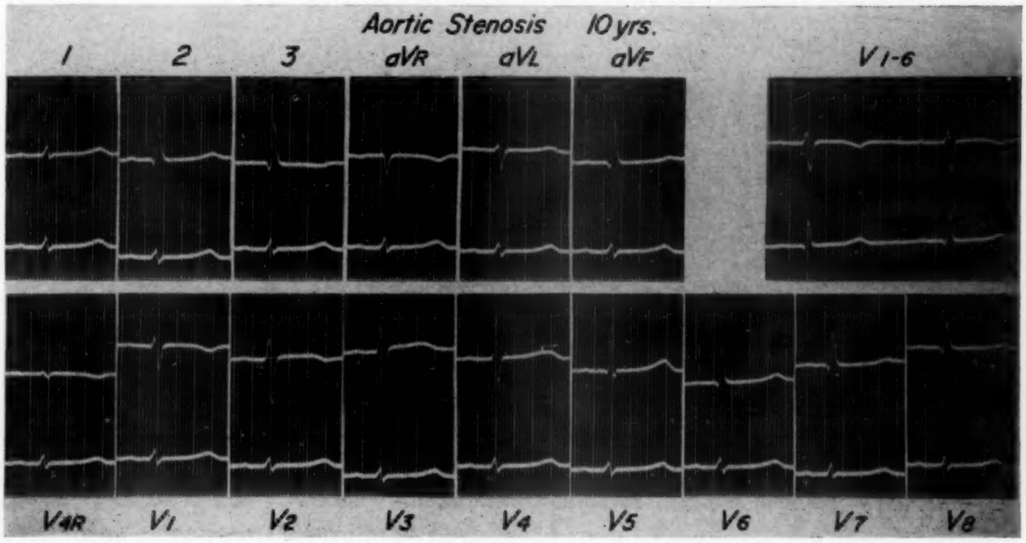


A.

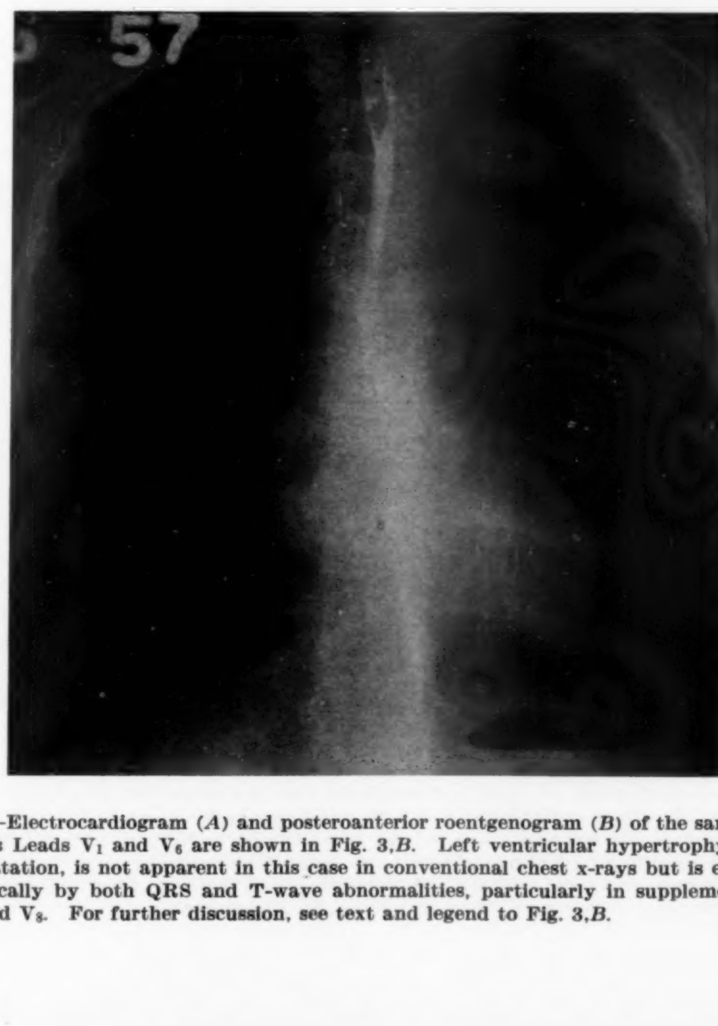


B.

Fig. 4.—Electrocardiogram (*A*) and posteroanterior roentgenogram (*B*) of the same patient whose simultaneous Leads V_1 and V_6 are shown in Fig. 3,*A*. Left ventricular enlargement, predominantly hypertrophy, apparent in this case in the chest x-ray, is evidenced electrocardiographically only by a primary increase in the positive amplitude of the T wave in leads from the left side of the precordium. There is, significantly, no evidence of associated left atrial enlargement and no increase in the positive amplitude of QRS (compare with Fig. 9,*A*).



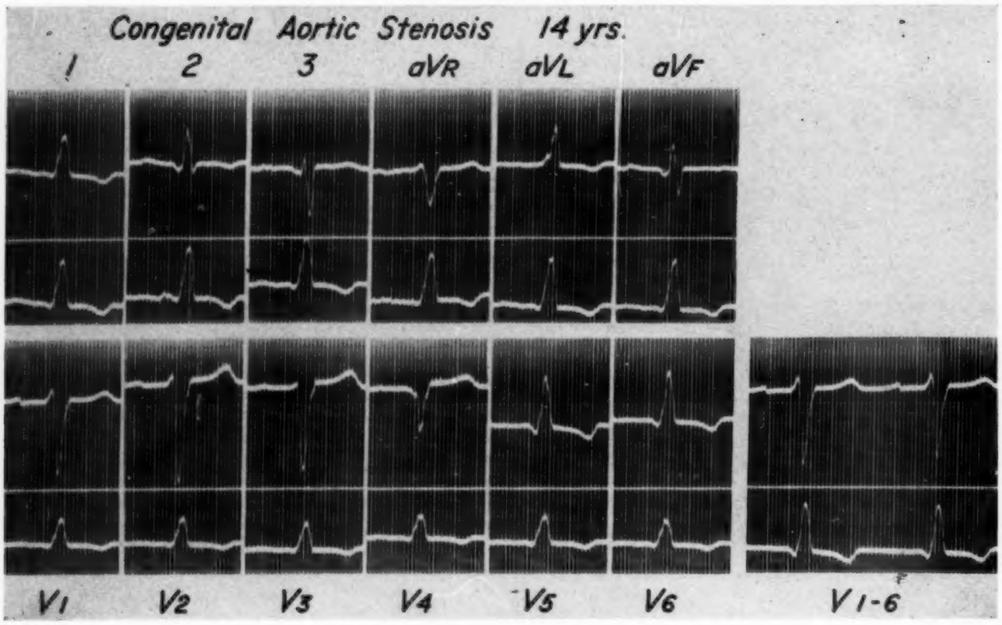
A.



B.

Fig. 5.—Electrocardiogram (*A*) and posteroanterior roentgenogram (*B*) of the same patient whose simultaneous Leads V_1 and V_6 are shown in Fig. 3,*B*. Left ventricular hypertrophy, without superimposed dilatation, is not apparent in this case in conventional chest x-rays but is evidenced electrocardiographically by both QRS and T-wave abnormalities, particularly in supplementary precordial Leads V_7 and V_8. For further discussion, see text and legend to Fig. 3,*B*.

A.



B.

Fig. 6.—Electrocardiogram (*A*) and posteroanterior roentgenogram (*B*) of a patient similar in every respect to the one whose simultaneous Leads V_1 and V_6 are shown in Fig. 3,*C*. This is, of course, the electrocardiographic pattern which has usually been referred to as "typical" of left ventricular enlargement of the so-called "systolic-overload" type, but without consideration of the quantitative aspect. In other words, completely different electrocardiographic patterns may be just as "typical," but of different quantitative degree, of the same hemodynamic abnormality.

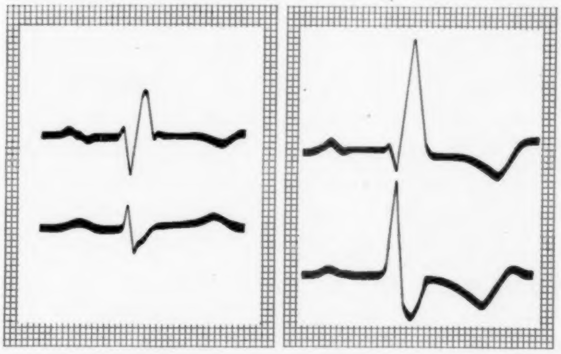
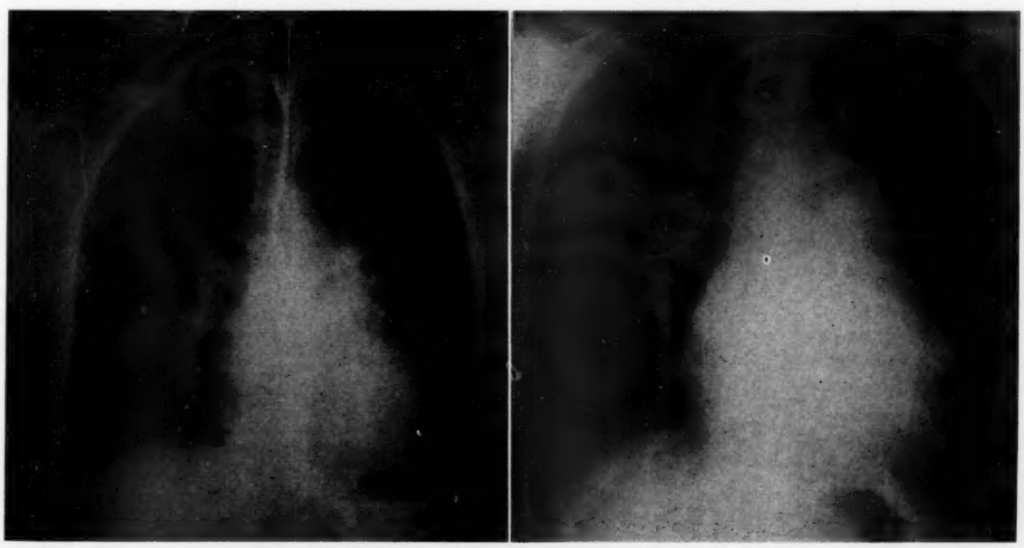
A.

B.

Fig. 7.—These two sets of simultaneously recorded precordial leads (V_1 above and V_6 below) represent different typical patterns observed in low-pressure communications with left-to-right shunting, in this case interatrial septal defect, with resulting enlargement of the right atrium and right ventricle. In *A*, the patient, aged 24 years, has only a slight elevation of right ventricular pressure (40/0-6 mm. Hg). The precordial lead pattern, as indicated by just Leads V_1 and V_6, would appear to be typical of relatively uncomplicated right bundle branch block plus a P-wave pattern indicative of probable right atrial enlargement. The remainder of the standard, and perhaps in addition supplementary, precordial leads are, of course, necessary for the adequate determination of electrocardiographic evidence of actual right ventricular enlargement in this type of situation. In *B*, the patient, aged 20 years, has in addition to the interatrial septal defect a marked degree of pulmonary artery and right ventricular hypertension (70/34 and 70/0-7 mm. Hg, respectively). The resulting increased degree of right ventricular hypertrophy is probably reflected electrocardiographically in the relatively large amplitude and late inscription time of the R′ deflection in Lead V_1, and right ventricular dilatation is reflected in the fact that variations in predominantly right epicardial potentials are observed as far to the left as Lead V_6. In the absence of a septal Q wave, T-wave inversion in left precordial leads is, therefore, not necessarily evidence of associated enlargement of the left ventricle, and this is another type of instance in which exploring leads farther to the left than the so-called "standard" positions are essential.



A. *B.*

Fig. 8.—These two posteroanterior roentgenograms correspond, respectively, to the electrocardiograms in *A* and *B* of Fig. 7. Both of these x-rays may be considered typical of the particular hemodynamic situation they represent, with increased volume of pulmonary blood flow and enlargement of the right atrium, right ventricle (dilatation as well as hypertrophy), and central pulmonary arteries. The electrocardiogram is of supplementary value here, primarily for its ability to indicate the presence or absence of associated left atrial or left ventricular abnormalities.

INTERPRETATION OF THE ELECTROCARDIOGRAM

For the accurate interpretation of the properly recorded electrocardiogram it is obvious that among the necessary requirements are included the following ones: (1) There must be complete standards of normal for all leads and at all ages. In this regard the importance of establishing separate standards for sufficiently small individual age increments, particularly during infancy and early childhood, must be emphasized. (2) In abnormal clinical situations any physiologic-anatomic correlations of the electrocardiogram, in order to be reasonably valid, must be based primarily if not exclusively on comparative studies of precisely similar (or equivalent) factors, including age, qualitative as well as quantitative hemodynamic variations, and, of course, structural malformation.

It must be obvious that failure to fulfill these basic principles may contribute and, indeed, already has contributed significantly to major differences of opinion regarding the clinical value of the electrocardiogram, whereas, by the same token, rigid adherence to such standards, together with the inclusion of statistically significant numbers of cases within each appropriate category, should go far toward the actual realization of the fullest potential of this clinical diagnostic technique.

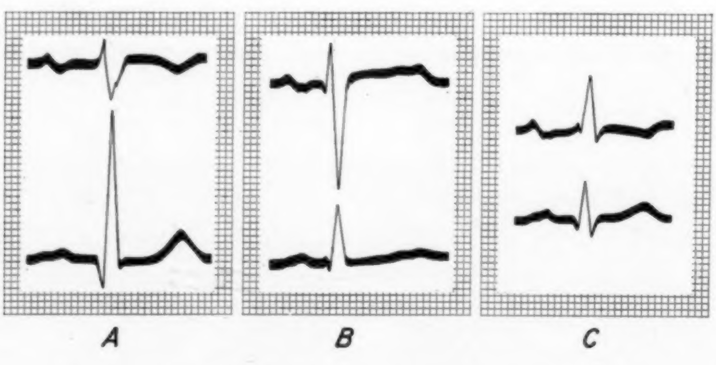
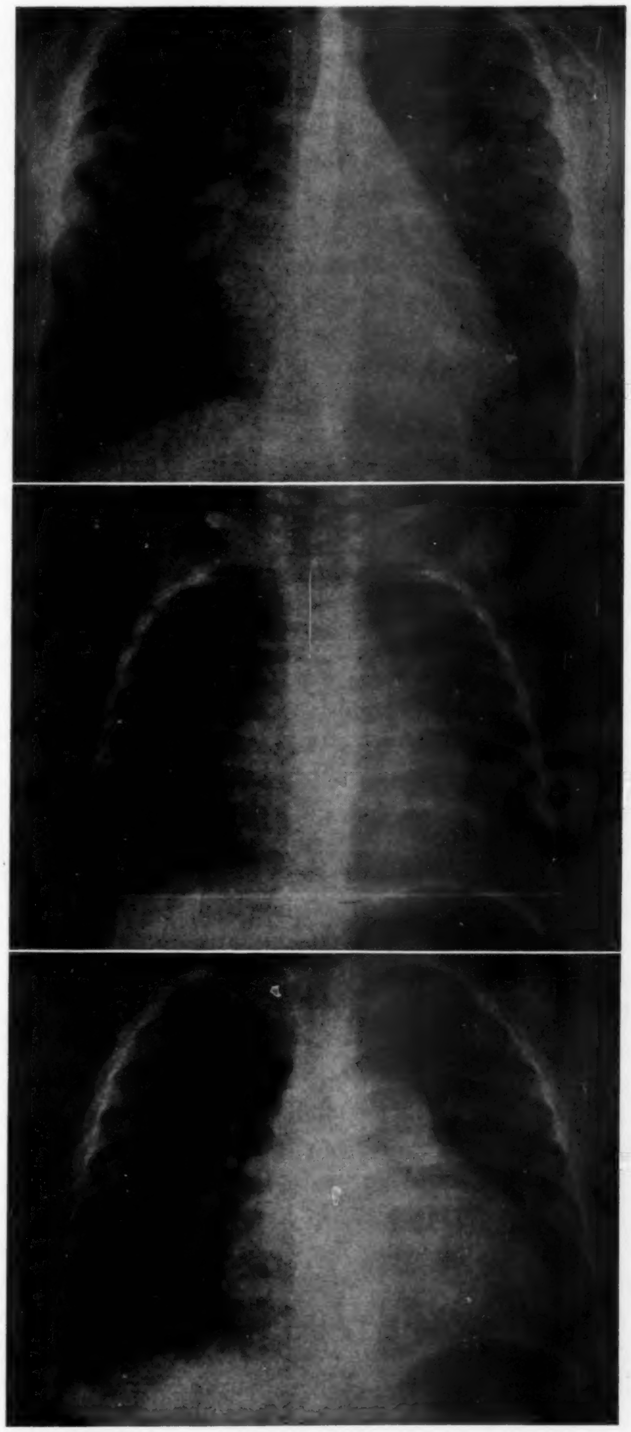


Fig. 9.—These three sets of simultaneously recorded precordial leads (V_1 above and V_6 below) represent several typical patterns observed in high-pressure communications with left-to-right shunting, in this case interventricular septal defect. These are, furthermore, representative of increasing degrees of pulmonary artery and right ventricular hypertension, but all due at least in part to increased volume of pulmonary blood flow. The ages of the patients represented are: *A*, 5 years; *B*, 4 years; *C*, 2 years. In *A*, the principal electrocardiographic features are increased positive amplitude of both RS and T in leads from the left side of the precordium, together with a P-wave pattern indicative of associated enlargement of the left atrium. These features are considered typical of a moderate degree of increased volume-flow work and the resulting enlargement (combined dilatation, that is, increased chamber volume, and hypertrophy) of the left ventricle. The normal form of the ventricular deflections in Lead V_1 makes it reasonably certain that there can be no great elevation of pulmonary artery or right ventricular pressure. In *B*, the precordial lead pattern is indicative of some degree of left bundle branch block plus left atrial enlargement. This type of ventricular complex, which occurs commonly in this particular hemodynamic situation, may be difficult to recognize without one of the following technical adjuncts to routine electrocardiography: (1) simultaneous leads, (2) some form of amplification, and (3) increased film-paper speed. In *C*, the ventricular deflections in Lead V_1 are indicative of right ventricular enlargement, possibly combined hypertrophy and dilatation (right ventricular pressure measuring 76/0-5 mm. Hg). The electrocardiographic detection of left ventricular enlargement here is perhaps not quite so certain. The P-wave pattern, however, is exceedingly helpful by indicating left atrial enlargement (frequently in the absence of radiographic evidence of enlargement of this chamber) and, therefore, increased volume of pulmonary blood flow as a major factor in the genesis of the pulmonary artery hypertension.



A.

B.

C.

Fig. 10.—These three posteroanterior roentgenograms correspond, respectively, to the electrocardiograms in *A*, *B*, and *C* of Fig. 9. All of the chest x-rays display evidence of increased volume of pulmonary blood flow and, despite the variations in the contour of the heart, some type of cardiac enlargement. In these particular cases a combination of radiographic and electrocardiographic information is exceedingly helpful.

The next fundamental questions which must be considered are these: (1) On what basis may one presume to interpret an electrical record in such specific and qualitatively different terms as physiologic work and anatomic size, and this with particular reference to individual chambers of the heart? (2) Assuming, even with certain qualifications (which are equally important to specify), the validity of the proposed correlations, what are the characteristic features of the electrocardiogram which permit such specific interpretation?

In answer to the first question, and assuming that the heart (or, more specifically, the myocardium) is otherwise normal, certain "known" or at least assumed facts regarding cardiac electrophysiology may be considered as basic: (1) Regardless of the exact spatial, and possibly even the temporal, sequence of ventricular depolarization, the form of the QRS complexes, including the magnitude of voltage generated and the duration of time required for myocardial activation, probably depends at least in part on the total length of the pathway traversed (ventricular volume) and on the endo-epicardial thickness of the myocardium. (2) The T wave of the electrocardiogram is known to be influenced primarily by such functional factors as increased intraventricular pressure, without necessarily any accompanying anatomic changes, such as demonstrably increased cardiac chamber size, and therefore without necessarily any accompanying abnormalities of the QRS. (3) An as yet somewhat limited comparison between the semidirect precordial leads and those taken directly from the epicardial surface of the heart would appear to support the assumption that the form of the variations in potential recorded in the former bear a fundamental resemblance to the form of those occurring at the surface of each ventricle. Even though direct leads from the epicardial surface of the heart represent mixtures of near and distant myocardial de- and repolarization effects, the variations in potential recorded in either direct or semidirect leads may probably be considered representative of electrical activity occurring predominantly in the region of the heart lying nearest to the exploring electrode.

In answer to the second question, a correlated analysis of clinical, radiographic, physiologic, and anatomic data with that derived from the electrocardiogram would appear to validate within reasonable and recognized limits the following basic interpretations: (1) The earliest recognizable primary electrocardiographic sign of increased intraventricular (systolic and mean) pressure, and, more specifically, increased pressure-work, is isolated increased T-wave positivity, either relative or absolute, in leads facing the epicardial surface of the ventricle in question. This sign may be present when there is ventricular hypertension without anatomically demonstrable muscular hypertrophy, or it may characterize myocardial hypertrophy before there is any increase in cardiac chamber volume and therefore prior to the occurrence of any enlargement as determined clinically or radiographically. Since this is also most clearly evident before the development of characteristic changes in the configuration of the initial ventricular deflections (QRS), it may in this degree constitute the only clinical diagnostic sign of this specific hemodynamic abnormality. (2) With a more advanced degree of increased pressure-work, actual myocardial hypertrophy, that is, increased muscle thickness without a significantly increased

chamber volume, becomes evident electrocardiographically by an increased positive area inscribed under QRS (increased amplitude or delayed inscription time of RS, or both) in leads facing the epicardial surface of the ventricle in question. Conventional radiography may or may not provide specific information diagnostic of single-chamber enlargement of this hemodynamic type and quantitative degree. The T-wave pattern in the precordial leads, which at first reflected primary changes alone, may now display additional changes which may be considered, at least in part, secondary to those occurring in the accompanying QRS complex. (3) By contrast with the preceding (that is, hypertensive work with resulting simple "concentric" hypertrophy but no essential increase in ventricular chamber volume, and usually no associated atrial enlargement) and beginning with the initial quantitative phase, increased ventricular work due to increased volume-flow is probably evidenced anatomically by increased chamber volume as well as muscular hypertrophy. Representative electrocardiographic patterns include those resembling if not actually representing bundle branch block (especially right but not infrequently left) or, particularly as in the case of the left ventricle, an increased positive amplitude (probably proportionate) of both QRS and T. This type of ventricular enlargement is more likely to be detected radiographically, even in relatively minimal degrees, than is that due to hypertension and hypertrophy alone. This hemodynamic situation is also more likely to be characterized by atrial as well as ventricular enlargement at all quantitative levels. (4) With marked degrees of either basic hemodynamic type of increased ventricular work the resulting anatomic enlargement consists of both hypertrophy and dilatation, and the electrocardiogram correspondingly displays mixed or combined patterns which appear to be dominated more by the quantitative degree than by the specific hemodynamic origin of the enlargement. The clinical and, more specifically, radiographic problem here is not so much the determination of the presence of cardiac enlargement but rather that of differentiating right from left or determining and quantitating the presence of combined right and left cardiac chamber enlargement.

SUMMARY AND CONCLUSIONS

At least potentially, and to an already great extent actually, a properly recorded and accurately interpreted electrocardiogram probably provides the most specific clinical index to not only the presence but also the basic hemodynamic type, and to a certain extent the degree, of increased single or combined cardiac chamber work and its resulting anatomic enlargement.

Specific electrocardiographic criteria are summarized briefly and illustrated as to simple basic patterns.

Ethnic Group Differences in Coronary Heart Disease in Singapore: An Analysis of Necropsy Records

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The use of mortality data obtained from published or other reports of official national agencies as an indication of the prevalence of arteriosclerotic heart disease in a country, and the extended use of such data for comparing prevalence in different countries[1-4] or in different geographic areas of the same country[5] raise several questions. How precisely do deaths from arteriosclerotic heart disease reflect the true prevalence of this disease? How accurately do reported death figures represent actual deaths from this condition? How comparable are these reported data from country to country? Yerushalmy and Hilleboe[6] have pointed out some of the limitations in using these mortality data. Differences in proportions of deaths which have causes certified by medical practitioners, and differences in levels of medical practice, in the usage of terms when assigning cause of death,[7] and in ways of classifying causes of death may all contribute to limiting the value of such data for comparative purposes.

A more direct way of measuring the incidence of arteriosclerotic heart disease for comparison between groups is to analyze the prevalence found at postmortem examination. The major difficulty here lies in the selection that often goes into hospital necropsy series. This selection, as pointed out by Berkson,[8] tends to make hospital populations unrepresentative of the general population of sick persons. Mainland[9] has shown how complex are the factors that contribute to the resulting bias. Another difficulty that arises comes from observer differences in the definition of what degree of coronary atheroma is to be regarded as "significant" and in ensuring that when present it is noted.

It is suggested by the writers that under certain circumstances, such as those described below, necropsy data may be analyzed in order to make useful comparisons of the prevalence of arteriosclerotic heart disease between groups

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Received for publication April 20, 1959.

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of persons. The study recorded here indicates differences in prevalence of the disease in two distinct ethnic groups in Singapore: Chinese with a low prevalence of coronary heart disease and Indians with a relatively high prevalence. Reasons are given why the writers consider that there is some validity in this comparison, and the suggestion is made that samples from these two ethnic groups may be suitable for further study of etiological factors.

MATERIAL AND METHODS

This study was carried out on records of necropsies performed by the Department of Pathology, Government Medical Service, Singapore, during the period 1950 to 1954, and had as its aim the obtaining of data on the prevalence of cardiovascular disease. The civilian population of

TABLE I. NECROPSIES PERFORMED IN SINGAPORE, 1950 to 1954, ACCORDING TO SEX AND ETHNIC GROUP OF SUBJECT

SEX AND ETHNIC GROUP	NUMBER OF NECROPSIES		NECROPSIES AS PER CENT OF DEATHS OCCURRING IN THE RESPECTIVE SEX AND ETHNIC GROUPS, 1950-1954	
Males: Total		6,375		16.2
Chinese	5,326		21.0	
Indians*	655		24.9	
Malaysians	150		2.8	
Others	244		27.8	
Females: Total		3,193		12.9
Chinese	2,902		15.7	
Indians*	159		12.5	
Malaysians	44		1.0	
Others	88		17.0	

*In this and subsequent tables the ethnic group *Indian* includes a small number of Pakistanis.

TABLE II. PROPORTION OF NECROPSIES TO DEATHS AMONG CHINESE AND INDIAN MALES (BY AGE GROUP) IN SINGAPORE, 1950 to 1954

AGE GROUP	0–9	10–19	20–29	30–39	40–49	50–59*	60–69*	70* AND OVER
Number of Deaths								
Chinese	9,884	687	958	1,646	3,081	3,900	3,339	1,862
Indians	901	40	169	361	461	390	222	88
Necropsies as Percentage of Deaths								
Chinese	24.3†	42.5	35.9	27.9	22.6	17.9	10.0	4.8
Indians	8.9†	32.5	45.6	42.1	34.5	31.5	19.4	4.5

*See text for method of obtaining numbers in these columns.

†The disproportionately high percentage of Chinese aged 0-9 years coming to necropsy, as compared with Indians, is due to the large number of Chinese bodies of this age group that are unclaimed by relatives.

Singapore numbered 1,445,929 at the latest census in 1957, and consisted of 75.4 per cent Chinese, 13.6 per cent Malays and other Malaysians, 8.6 per cent Indians and Pakistanis, and 2.4 per cent other ethnic groups.[10] Hospital services for this population are provided mainly by government hospitals, comprising one large general hospital and several special hospitals for tuberculosis, maternity and gynecological cases, leprosy, venereal disease, infectious diseases, and mental disorders; no hospital fees are charged except to a minority of patients who choose to be admitted to paying wards. The proportion of the population served by private hospitals is small. All necropsies done in Singapore, with the exception of a small number performed on personnel of the United Kingdom Armed Forces, are performed by, and recorded in, the Department of Pathology. This gives island-wide coverage and includes not only cases that come to postmortem examination from all hospitals, but all coroner's cases as well. Table I gives, according to sex and ethnic group, the number of bodies that were examined post mortem, and the percentage that this number formed of the total number of persons in the respective sex and ethnic group who died during the period 1950 to 1954. In this study the Indian ethnic group includes a small number of Pakistanis. In Table II the proportion of necropsies to total number of deaths for Chinese and Indian males is given by age group. The number of deaths is not available separately for the age groups 50 to 59, 60 to 69, and for 70 and over, for the years 1950 and 1951. The death figures shown in Table II, therefore, include estimated ones for these decennia, calculated by applying the proportions that obtained for these age groups during the years 1952 to 1954 to the total deaths over the age of 50 during 1950 and 1951.[11]

Postmortem examination included an inspection of the coronary arteries, heart, and large vessels in nearly all instances, but the skull was not opened in every case. Necropsies were done by several pathologists, but any observer difference that may have arisen was evened out by the bodies being distributed among the observers randomly in respect to ethnic group and age.

When a cardiovascular condition was noted in the necropsy record, irrespective of whether or not it was related to the cause of death, it was entered into the record card under one of the rubrics, *first heart disease, second heart disease, third heart disease*, or *fourth heart disease*. If a single cardiovascular abnormality was found, it was listed under first heart disease. Where more than one cardiovascular condition was present in the same individual, the condition entered under the rubric *first heart disease* was the one found to be the underlying cause of death[12,13] or, if death was not caused by the cardiovascular condition, the condition judged to be the major abnormality present: other abnormalities were given second, third, or fourth place, again depending on which was assessed to be of more or less importance. In practice, difficulty in making these judgments arose in only a small number of cases.

The initial classification of cardiovascular disease used was extensive, and was based, with some minor modifications, on the World Health Organization's Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (sixth revision). The final diagnostic groupings chosen are given below, together with the Detailed List Categories to which they correspond.

Cardiovascular syphilis: 022, 023, syphilitic aneurysm of cerebral vessels (026).
Rheumatic heart disease: 401, 402.1, 410 to 416.
Coronary disease: 420. Note: Although provision was made in the initial classification for chronic endocarditis (421) not specified as rheumatic, syphilitic or due to gonorrhea, and for myocardial degeneration with arteriosclerosis (422.1), these terms did not appear in the necropsy records. When fatty degeneration of the heart (422.0) and nonarteriosclerotic myocardial degeneration occurred in the records, these were entered under "other heart disease."
Arteriosclerosis: 450.
Hypertensive disease: 440 to 443, 445 to 446.
Vascular lesions of the central nervous system: 330 to 332, 334, and congenital aneurysm (754.6).
Cor pulmonale: From category 434.3 and including 434.0.
Other heart disease covered all other cardiovascular abnormalities not including peripheral vascular disease, but including congenital malformations of the circulatory system (754) except congenital cerebral aneurysm; acute endocarditis (430); acute pericarditis (018.2, 432); acute myocarditis and myocardial degeneration (431, 422.0 and 422.2 when not of arteriosclerotic origin); nonsyphilitic aortic and other aneurysms (451, 452); pulmonary embolism, infarction or thrombosis (465 as well as those of puerperal origin); cardiac beriberi (280); thyrotoxic

heart disease (252); neoplasms of the heart and pericardium (197, 199, 227, 229, 238, 239); traumatic heart disease (N861) and other heart conditions (034 and 434 excluding 434.0 and cor pulmonale).

FINDINGS AND DISCUSSION

In this report, only data referring to male Chinese and Indians will be discussed, because the number of Malaysians who came to necropsy was small, and the group labeled "Others" comprised persons from a great variety of ethnic groups. The data for female Chinese and Indians are placed on record, but owing to the small number of Indian females involved, no conclusions can be drawn from these figures.

Table III shows the percentage of cases in which evidence of cardiovascular disease was found at necropsy, divided into specific categories of heart disease and age groups. The prevalence of cardiovascular disease in Indian males between the ages of 20 and 69 years appears to have been higher than in Chinese

TABLE III. POSTMORTEM EVIDENCE* OF CARDIOVASCULAR DISEASE AMONG CHINESE AND INDIAN MALES IN SINGAPORE, 1950-1954, BY AGE GROUP AND SPECIFIC CATEGORY OF CARDIOVASCULAR DISEASE

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Chinese							
Total number of necropsies	292	344	459	696	700	334	89
Percentage with:							
Cardiovascular syphilis	0.7	2.0	5.7	7.6	9.6	6.9	6.7
Rheumatic heart disease	5.8	2.0	2.2	2.0	1.1	0.9	2.3
Coronary disease	0.3	1.2	3.5	4.5	6.0	7.5	10.1
Arteriosclerosis	1.4	0.9	3.9	5.9	11.3	15.9	21.4
Hypertensive disease	0.3	0.3	5.0	4.5	4.9	5.7	5.6
Vascular lesions of C.N.S.	0	0	0.9	1.4	1.9	2.4	4.5
Cor pulmonale	0.3	0.3	1.3	2.6	5.0	4.2	4.5
Other heart diseases	5.6	5.5	3.0	2.8	4.2	0.5	1.1
Percentage with evidence of cardiovascular disease	14.4	12.2	25.5	31.3	44.0	48.2	56.2
Indians							
Total number of necropsies	13	77	152	159	123	43	4
Percentage with:							
Cardiovascular syphilis	0	1.3	5.9	3.1	4.1	4.7	25.0
Rheumatic heart disease	7.7	0	0	2.5	2.4	0	0
Coronary disease	0	9.1	19.7	28.3	29.3	25.6	50.0
Arteriosclerosis	0	2.6	5.3	7.6	6.5	20.9	0
Hypertensive heart disease	0	2.6	3.3	5.7	7.3	7.0	0
Vascular lesions of C.N.S.	0	1.3	0	1.3	4.9	2.3	0
Cor pulmonale	0	1.3	1.9	2.5	2.4	9.3	25.0
Other heart diseases	0	1.0	2.7	3.1	1.6	6.9	0
Percentage with evidence of cardiovascular disease	7.7	18.2	38.8	54.1	58.5	76.7	100.0

*This includes first heart disease only.

males of corresponding age. This differential may be accounted for almost entirely by the more frequent occurrence of coronary disease among Indians. Coronary disease formed approximately 50 per cent of all heart disease in Indian males above the age of 20 years, whereas in male Chinese it formed between 10 and 20 per cent. When the figures for coronary disease are separated out, there remains little difference between male Indians and Chinese over the age of 20 in the percentages for all other noncoronary forms of heart disease (Table IV).

TABLE IV. COMPARISON BETWEEN CHINESE AND INDIAN MALES AS TO THE PREVALENCE* OF CORONARY DISEASE AND ALL OTHER FORMS OF CARDIOVASCULAR DISEASE, BY AGE GROUPS

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Chinese							
Percentage of necropsies with:							
Coronary disease	0.3	1.2	3.5	4.5	6.0	7.5	10.1
All other cardiovascular diseases	14.1	11.0	22.0	26.8	38.0	40.7	46.1
Total cardiovascular disease	14.4	12.2	25.5	31.3	44.0	48.2	56.2
Indians							
Percentage of necropsies with:							
Coronary disease	0	9.1	19.7	28.3	29.3	25.6	50.0
All other cardiovascular diseases	7.7	9.1	19.1	25.8	29.2	51.1	50.0
Total cardiovascular disease	7.7	18.2	38.8	54.1	58.5	76.7	100.0

*This includes first heart disease only.

Tables III and IV are derived from an analysis of conditions listed under the rubric *first heart disease* only. The data in these tables suffer from the disadvantage that when more than one cardiovascular condition was present in the same individual, the selection of one disease for entry under the rubric *first heart disease* necessarily displaced the other diseases into the positions of second, third, or fourth heart disease. To see whether other cardiovascular conditions, for example, syphilis, were masking the presence of coronary disease, an analysis was made for total prevalence of coronary disease entered under any one of the four rubrics, first, second, third, or fourth heart disease. It was found, as Table V indicates, that this had occurred to a certain degree, but that the differential between Indians and Chinese was still marked.

A possible source of error may have arisen in the assessment of the degree of coronary atheroma regarded as significant when myocardial involvement was not apparent. It has already been noted that necropsies were performed by a number of pathologists, but that the cadavers were distributed among them randomly in respect to ethnic group and age. In Table VI the total prevalence of coronary disease is divided into two categories, the first being uncomplicated

coronary disease in which the arteries alone were involved, and the other being complicated coronary disease, that is, coronary heart disease, which included those cases in which coronary atheroma, with or without thrombosis, was associated with myocardial infarction, necrosis, fibrosis, or aneurysm. This second category is equivalent to the ischemic heart disease defined by the World Health Organization Study Group on Atherosclerosis and Ischemic Heart Disease.[14] It appears from Table VI that the differences between the two ethnic groups for coronary atheroma alone were small, and that the higher prevalence of coronary disease among Indians as shown up in this necropsy series was due mainly to complicated coronary disease, that is, coronary heart disease. The question that immediately arises is whether the high percentages of coronary heart disease

TABLE V. TOTAL PREVALENCE* AT NECROPSY OF CORONARY DISEASE AMONG CHINESE AND INDIAN MALES, BY AGE GROUP

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Coronary Disease as First Heart Disease: Percentage of Necropsies							
Chinese	0.3	1.2	3.5	4.5	6.0	7.5	10.1
Indians	0	9.1	19.7	28.3	29.3	25.6	50.0
Coronary Disease Present at Necropsy, Whether First, Second, Third, or Fourth Heart Disease: Percentage of Necropsies							
Chinese	0.3	2.3	7.0	10.0	14.4	15.6	18.0
Indians	0	10.4	23.0	34.6	36.6	44.2	75.0

*This includes first, second, third, and fourth heart disease.

TABLE VI. COMPARISON OF UNCOMPLICATED CORONARY DISEASE AND COMPLICATED CORONARY DISEASE* AMONG CHINESE AND INDIAN MALES, BY AGE GROUP

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Percentage of Necropsies With Uncomplicated Coronary Disease†							
Chinese	0	1.4	4.2	6.3	9.4	9.3	10.1
Indians	0	2.6	4.6	7.5	12.2	23.3	25.0
Percentage of Necropsies With Complicated Coronary Disease†							
Chinese	0.3	0.9	2.8	3.4	5.0	6.3	7.9
Indians	0	7.8	18.4	27	24.4	20.9	50.0

*Based on total prevalence, i.e., first, second, third, and fourth heart disease.
†For definitions see text.

among Indians were due to selective rates for admission of Indians into hospital, with or without further selective rates for postmortem examination, or, contrariwise, whether the low prevalence among Chinese was the result of some bias that kept Chinese patients with coronary heart disease out of hospital and out of the postmortem series. The problem of selection or bias will be discussed below.

Data for females are recorded in Table VII. Differences between Chinese and Indians again appear, although the prevalence percentages are at a lower level.

TABLE VII. POSTMORTEM EVIDENCE OF CARDIOVASCULAR DISEASE* AND OF CORONARY DISEASE† IN CHINESE AND INDIAN FEMALES, BY AGE GROUP

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Chinese							
Number of necropsies	170	194	192	205	148	93	43
Percentage with:							
Cardiovascular disease	16.5	13.9	16.1	25.9	32.4	48.4	62.8
Coronary disease	0	2.6	1.6	4.4	7.4	14.0	23.3
Indians							
Number of necropsies	12	23	28	13	7	8	1
Percentage with:							
Cardiovascular disease	16.7	8.7	35.7	30.8	85.7	75.0	100.0
Coronary disease	0	0	7.1	7.7	28.6	25.0	100.0

*This includes first heart disease only.
†Based on total prevalence, first, second, third, and fourth heart disease.

THE PROBLEM OF SELECTION OR BIAS

It is not possible to prove that hospital admission practices and selection for necropsy were not factors responsible for the marked differential in prevalence of coronary heart disease noted between Chinese and Indian males in this postmortem series. While hospital services are equally available to all sections of the population, the limiting factor being the degree of severity of an illness relative to the hospital beds available, equal use may not be made of these services by different sections of the population. However, if selective admission of Indians to hospital were an important operative factor in producing a higher prevalence of coronary heart disease, one would expect other acute or subacute cardiovascular conditions, which should have tended similarly to bring Indians to hospital, to have exhibited a corresponding differential. A scrutiny of Table III shows that this was not the case: the percentage prevalences for all noncoronary cardiovascular conditions are fairly comparable or do not show consistent or large differences. The marked differential exists only in respect to coronary heart disease.

Out of the total series of postmortem examinations, a certain number were done on coroner's cases. Coroner's cases in Singapore include the following: all persons in whom death has occurred or is suspected to have occurred from unnatural causes; bodies found dead and individuals dying suddenly and unexpectedly in instances in which there is no contributory evidence to indicate that death was due to natural causes; all inmates dying in prison or in mental hospitals; and some patients dying shortly after admission to hospital before a diagnosis can be made. All coroner's cases come to necropsy. Table VIII refers only to bodies brought into hospital dead, since it is thought that selective factors pertaining to ethnic groups would be least likely to operate in this specific category, and that this category comes nearest to representing the general population.

TABLE VIII. TOTAL PREVALENCE* AT NECROPSY OF CORONARY DISEASE AMONG CHINESE AND INDIAN MALES—CORONER'S CASES BROUGHT INTO HOSPITAL DEAD

AGE GROUPS	10–19	20–29	30–39	40–49	50–59	60–69	70 AND OVER
Number of Necropsies							
Chinese	108	137	174	260	277	137	28
Indians	2	42	77	74	53	19	1
Percentage With Evidence of Uncomplicated Coronary Disease†							
Chinese	0	1.5	2.9	1.9	1.8	2.9	3.6
Indians	0	2.4	1.3	2.7	13.2	15.8	0
Percentage With Evidence of Complicated Coronary Disease†							
Chinese	0.9	0	4.0	6.5	9.7	6.8	10.7
Indians	0	14.3	28.6	40.5	35.9	36.8	100
Coroner's Cases Brought in Dead, as a Percentage of Deaths in Respective Ethnic-Age Group							
Chinese	15.7	14.3	10.6	8.4	7.1	4.1	1.5
Indians	5.0	24.9	21.3	16.1	13.6	8.6	1.1

*This includes first, second, third, or fourth heart disease.
†For definitions, see text.

It may be seen from Table VIII that coronary heart disease was again distinctly more common in Indians than in Chinese. Relative to total deaths in each ethnic-age group from 20 to 69, twice as many Indians as Chinese were coroner's cases brought in dead. The reasons for this are not completely known, but one third to one half of the excess number of Indians in each age group was the result of coronary heart disease.

Data in Table IX are intended to support the thesis that the differences between Chinese and Indians in the incidence of coronary heart disease as noted

in the analysis of this postmortem series are valid and not merely the result of hospital and necropsy selection factors. The coronary disease mortality rates given in Table IX are based on coronary heart disease (420.1) as a cause of death certified by qualified medical practitioners (including coroner's cases)[15] in Singapore, 1954 to 1957. Causes of death in Singapore are recorded in the following ways: after certification by a physician (that is, a legally qualified medical practitioner) who has cared for the patient during his last illness, with or without a postmortem examination having been done (approximately 54 per cent of all deaths); by the coroner following a necropsy and an inquiry or an inquest (approximately 9 per cent); or by an inspecting officer who inspects the body, listens to the story given by the deceased's relatives or associates, and, if satisfied that

TABLE IX. AGE-SPECIFIC RATES OF DEATH AND MORTALITY DUE TO CORONARY DISEASE (420.1) AMONG CHINESE AND INDIAN MALES IN SINGAPORE*

AGE GROUPS	20-29	30-39	40-49	50-59	60-69	70 AND OVER
Age-Specific Death Rates Per 1,000						
Chinese	1.9	3.8	8.6	21.1	50.8	105.2
Indians and Pakistanis	1.6	3.1	6.6	16.9	39.1	63.0
Coronary Disease Mortality Rates Per 100,000 Per Year						
Chinese	1.9	8.8	17.1	67.4	175.7	192.5
Indians and Pakistanis	4.4	43.1	120.0	255.0	418.8	432.3

*Based on an average of death figures for the years 1954-1957, and on population figures for 1957. The figures for coronary disease are based on deaths certified by qualified medical practitioners, including coroner's cases. Data from Tye.[15]

TABLE X. PROPORTION OF DEATHS IN MALES IN SINGAPORE IN WHICH CAUSE OF DEATH WAS CERTIFIED BY MEDICALLY QUALIFIED PRACTITIONERS (INCLUDING CORONER'S CASES), 1954-1957*

AGE GROUPS	20-29	30-39	40-49	50-59	60-69	70 AND OVER
Number of Deaths						
Chinese	599	858	1,958	3,203	3,093	1,803
Indians and Pakistanis	110	257	365	411	215	88
Percentage With Cause of Death Certified by Medically Qualified Practitioner or Coroner						
Chinese	87.5	87.8	81.5	73.2	67.1	54.0
Indians and Pakistanis	96.4	90.7	91.5	85.4	74.9	62.5

*Based on figures supplied by Tye.[15]

death has been due to natural causes, assigns a cause of death (approximately 37 per cent). Inspecting officers in the city of Singapore are hospital assistants (equivalent of male nurses) who have had some hospital training and possess limited medical knowledge, but outside the city limits the inspecting officers are police officers with no medical training. Owing to the inaccuracy of causes of death certified by such inspecting officers, data in Table IX have been based only on death certificates given by qualified medical practitioners, including coroner's cases. Table IX shows that, notwithstanding the fact that age-specific death rates for male Indians (and Pakistanis) were consistently somewhat less than corresponding rates for male Chinese, age-specific coronary mortality rates were significantly higher among male Indians in each age group. The validity of these figures may be questioned, when one notes that causes of death are certified by qualified medical practitioners and the coroner in only about two thirds of the total number of deaths in Singapore. It may be seen from Table X, however, that in the ethnic-age groups with which we are concerned a much higher percentage of deaths is thus certified. Furthermore, although it is possible that some deaths from coronary heart disease may have occurred in male Chinese (and male Indians as well) in whom the causes of death were recorded by inspecting officers, it is unlikely that their number was large, because the inspecting officer's work is usually done among the lowest socioeconomic groups, in which coronary heart disease is least likely to occur in Singapore.

CONCLUSION AND SUMMARY

In investigations into possible influences in the causation of coronary disease, a major difficulty has been to obtain a comparison group that is healthy, and not, in fact, one in which there is latent coronary artery disease, undiagnosed because of limitations in our methods of detecting it. The same difficulty applies to direct studies on individuals. It is suggested that samples from the Indian and Chinese population groups in Singapore may serve as suitable study and comparison groups, because a study of the occurrence of cardiovascular disease as found at postmortem examination has indicated that there is a low prevalence of coronary disease among Chinese, but a relatively high prevalence among Indians. It is argued that this differential is a valid one, and not merely due to selective ante- or postmortem factors. This differential in prevalence merits further investigation, particularly in view of the fact that the Chinese and Indians are culturally distinct groups living within the same physical environment and, therefore, offer a potentially more productive and less difficult basis for study than is given by groups living in different countries.

We are most grateful to Dr. L. S. da Silva, Senior Pathologist, Department of Pathology, Government Medical Service, Singapore, for permission to study the necropsy records of his department; to Dr. Enid Charles, World Health Organization Visiting Lecturer in Biostatistics, Department of Social Medicine and Public Health, University of Malaya, for devising the record card used in this study; to Mr. E. J. Philips, Chief of the Department of Statistics, Singapore, for the use of facilities in his department; to Miss D. E. Mitchell for the sorting and computation of data, and to Mr. Tye Cho-Yook, Lecturer in Biostatistics, Department of Social Medicine and Public Health, University of Malaya, for the data used in Tables IX and X.

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Aortic Stenosis: A Study With Particular Reference to an Indirect Carotid Pulse Recording in Diagnosis

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The diagnosis of aortic stenosis is often difficult. A systolic murmur at the base of the heart is common in the elderly and frequently defies identification by the available clinical aids. Reliance upon the classic criteria of a harsh systolic murmur and thrill, a diminished aortic second sound, and narrow pulse pressure may account, in part, for the poor showing in the reported clinico-pathologic correlations.

Bergeron and associates[1] reviewed 100 cases of aortic stenosis from autopsy material. They observed that, even in the presence of severe stenosis, there was frequently a normal aortic second sound, whereas a systolic thrill and murmur at the base were often absent. A harsh systolic murmur, heard loudest or exclusively at the apex, was at times the only physical finding. The antemortem diagnosis was missed in one half of the cases studied.

Mitchell and associates[2] analyzed 533 cases of aortic stenosis, of which 214 were culled from autopsy files. They noted that the systolic murmur was louder at the apex in 16 per cent of their cases. The loudness of the aortic murmur did not correlate with the severity of the stenosis, and in a number of patients with marked stenosis there was only a faint murmur.

At the present time, catheterization of the left heart appears to offer the most precise means of detecting the presence and estimating the degree of aortic stenosis.[3,4] However, this procedure is not without danger[5-7] and is not suitable for widespread clinical use.

Other diagnostic aids have included detection of aortic leaflet calcification by fluoroscopy[8] and tomography,[9] phonocardiographic demonstration of a diamond-

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Supported in part by a grant-in-aid from the United Air Lines Foundation, Chicago, Ill., and G. D. Searle & Co., Skokie, Ill.

Received for publication May 11, 1959.

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shaped murmur,[10] indirect recordings of the carotid and subclavian pulse,[11,12] and intra-arterial recording of the brachial pulse.[13]

In this communication we wish to report our experience with an indirect recording of the carotid pulse in a group of control subjects and in 70 patients with aortic stenosis, and to review partially the literature pertaining to the usefulness of pulse tracings in the diagnosis of aortic stenosis. The clinical observations on the patients studied are included.

REVIEW OF THE LITERATURE

It has been demonstrated in experimental animals that the central aortic pressure curve is altered when the aortic orifice is reduced to less than one quarter of its normal size.[14] This alteration is characterized by a short, sharp rise terminating in a V-shaped anacrotic notch, following which the pressure rises slowly, with irregular vibrations superimposed upon the basic contour of the curve.[15] However, in another experimental study,[16] systolic vibrations in the central aortic pulse were found in mild as well as in severe stenosis. The characteristics of the central pulse are propagated into the peripheral arteries.[17]

In a study of 23 patients, Grishman and associates[11] found the carotid pulse contour to be one of the most helpful diagnostic aids. The carotid pulse was recorded indirectly by a method that was not described. Feil and Brofman[12] recorded subclavian and radial pulse tracings in 10 patients with congenital subaortic stenosis. The tracings were recorded by means of a cup-tambour system, using a Frank segment capsule and Wigger's method of optical registration. They concluded that the absence of the dicrotic notch indicated valvular stenosis; its presence indicated subaortic stenosis. There was no anatomic confirmation of the diagnosis in either of these series.

Goldberg and associates[13] studied the pulse curves in 26 patients with predominant aortic stenosis confirmed at surgery. The pulse was recorded intra-arterially from the brachial artery. They concluded that the pressure curve was characteristic and emphasized the value of the Valsalva maneuver in bringing out the anacrotic phenomenon. Subsequently, the same group[18] reported that there was no consistent relationship between the degree of stensosis and the position of the anacrotic notch in the brachial artery pressure tracing, or the time interval from onset to the peak of systole.

Duchosal and associates[19] recorded the carotid pulse tracing in 28 patients with aortic stenosis by means of a differential manometer attached to a cuff placed around the patient's neck. The recording system had a linear response without phase distortion from 0 to 60 cycles per second. They concluded that the pulse tracing of aortic stenosis is characterized by slowing of the upstroke, a delayed single summit with superimposed vibrations, and straightening of the descending limb. The interval from the onset to the halfway point on the slanted upstroke was measured and appeared to correspond to the degree of stenosis. The interval was not modified by concomitant aortic insufficiency or mitral stenosis. Postmortem confirmation of the aortic stenosis was obtained in one of the 28 patients.

MATERIAL AND METHODS

The apparatus used in this study has been described previously.[20] It consists of a cup applicator mounted on a neckpiece and placed directly over the carotid artery. From the cup applicator a thin, flexible, rubber tubing is led into a crystal-type pickup which reproduces an electrical signal proportional to the change in pressure in the tubing. A tubing 4 feet long has a resonant frequency of 70 to 80 cycles, the resonant frequency being related directly to the tubing length. The apparatus is, in effect, a tuned system resembling a Helmholtz resonator. In Fig. 1 the frequency response of this type of a system is illustrated, comparing a tubing 8 feet long with a tubing 2 inches long. The resonant frequency may be determined by connecting the tubing to a microphone and a recorder and measuring the response at different induced frequencies.

A Sanborn Twin-Beam photographic recorder was used. Carotid pulse tracings and phonocardiograms were made at a paper speed of 75 mm. per second with an open bell and the Sanborn microphone. A stethoscopic amplifier was employed in all cases unless otherwise specified.

The carotid pulse contour obtained from a normal individual is shown in Fig. 2. The pulse contour of aortic stenosis is characterized by systolic vibrations superimposed upon a plateaued contour and is illustrated in Fig. 3 (Cases No. 2 and No. 4 of Group I).

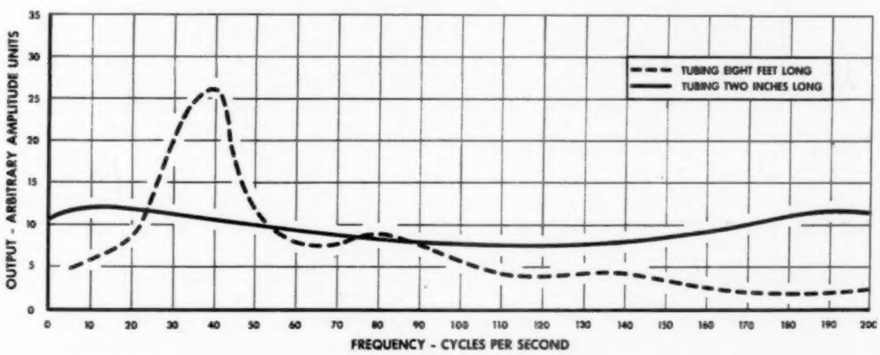

Fig. 1.—Frequency response of the crystal pickup as related to the length of tubing. Tubing 8 feet long, as illustrated, has a resonant frequency of 40 cycles. The resonant frequency of the tubing doubles by decreasing tubing length to 4 feet.

With the subject's head slightly turned to one side and tilted backward, the cup applicator is placed snugly over the carotid artery just below the angle of the mandible. It is helpful to record under vision with an oscilloscope to determine optimum placement of the cup. Recordings should be obtained from both carotid arteries, since systolic vibrations are occasionally present on one side and not the other. This technique is not quantitative because the amplitude of the systolic vibrations is influenced by the placement of the cup, the pressure exerted, anatomic variations, and variable transmission through the tissues of the neck.

As control material, carotid pulse tracings were obtained in 180 normal subjects, 85 patients with nonvalvular heart disease, and 55 patients with valvular heart disease other than aortic stenosis.

Seventy individuals with aortic stenosis were studied. In general, the diagnosis was based upon the presence of a systolic murmur that was quite characteristic of aortic stenosis or a murmur that "could not be explained away" and therefore made us search for aortic stenosis. There were 2 patients with concomitant mitral stenosis in whom the basal systolic murmur was not thought to be that of aortic stenosis until the carotid pulse tracing was recorded. Most of the 70 patients were examined and followed up by one or two of us (I.H., J.M.E.) over a considerable period of time. In addition to the physical examination, each patient had fluoroscopic examination, roentgenograms of the heart, and an electrocardiogram.

The 70 patients were divided into two groups—those with fluoroscopically demonstrable aortic leaflet calcification (Group I) and those without it (Group II). The detection of aortic leaflet calcification was accepted as confirmation of the presence of aortic stenosis. Eleven of

the patients in Group I have died. Autopsy, performed in 7 of the 11, demonstrated aortic stenosis with leaflet calcification. In one other patient in this group, diagnosis was proved by left heart catheterization. In the subjects of Group II, autopsy was performed in one of the 3 patients who died, and confirmed the diagnosis. In another, during thoracotomy for the correction of a vascular ring, a systolic thrill was palpable over the ascending aorta; and in one other, aortic stenosis was verified at the time of aortic valve surgery.

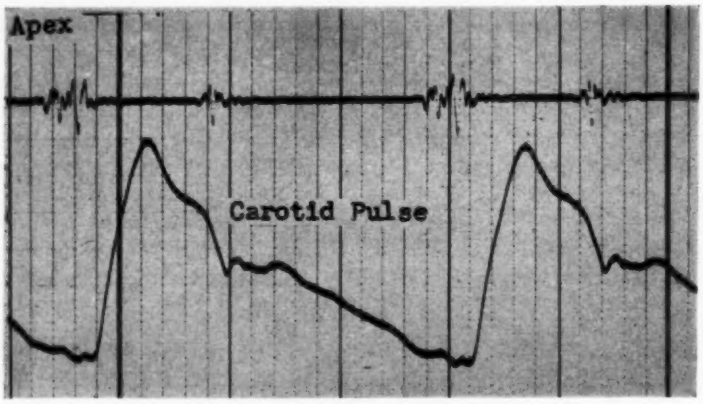

Fig. 2.—Pulse tracing of a normal young man.

FINDINGS AND COMMENT

Group I: Aortic Stenosis With Leaflet Calcification.—There were 25 patients in this group, ranging in age from 29 to 86 years (Table I). There were 5 females and 20 males. The pulse pressure was narrowed in only 3 patients (Cases 8, 14, and 16) with blood pressure readings of 110/88, 110/80, and 100/74 mm. Hg, respectively. There was an aortic diastolic murmur in 12 of the 25 patients. However, aortic regurgitation of hemodynamic significance was present in only 3 of the 12 with blood pressures of 140/50, 140/30, and 150/55 mm. Hg, respectively. Three of the 25 patients also had mitral stenosis. The diagnosis of mitral stenosis was based upon the typical auscultatory and roentgenographic findings and was confirmed eventually in all 3 patients at autopsy.

A systolic murmur was heard at the aortic area in all 25 patients. Some of the loudest murmurs occurred in individuals with hemodynamically significant aortic insufficiency, whereas the murmur of lowest intensity was found in a patient with recent myocardial infarction and left heart failure. It would appear that stroke volume and myocardial ejection forces are important factors in determining the loudness of the murmur. A systolic murmur was heard at the apex in all 25 cases, and in 9 it was equal to or louder than the murmur at the aortic area. A basal systolic thrill was present in 15 of the 25 subjects.

A diamond-shaped murmur was recorded at the aortic area in the phonocardiograms of 14 of the 25 patients. However, it was not consistently diamond-shaped in the same recording in 7 of the 14; in several this variation could be related to an irregular ventricular rate, the murmur becoming diamond-shaped only after the longer intervals of diastolic filling. The presence of the diamond-

shaped murmur appeared to be related to stroke volume and myocardial function. In the remaining 12 patients the murmur was of low intensity, with variable peaks, and was not diamond-shaped. The aortic second sound was diminished or absent in 19 patients and was normal in 6. It is of interest that the aortic first sound was similarly affected in 23 out of the 25 cases.

The characteristic systolic vibrations were present in the carotid pulse tracing in 24 of the 25 subjects. Carotid pulse contours typical of the subjects of Group I are illustrated in Fig. 3. The systolic vibrations of highest amplitude were seen in a 37-year-old asymptomatic pilot who also had hemodynamically significant aortic regurgitation (Case 18, Fig. 4).

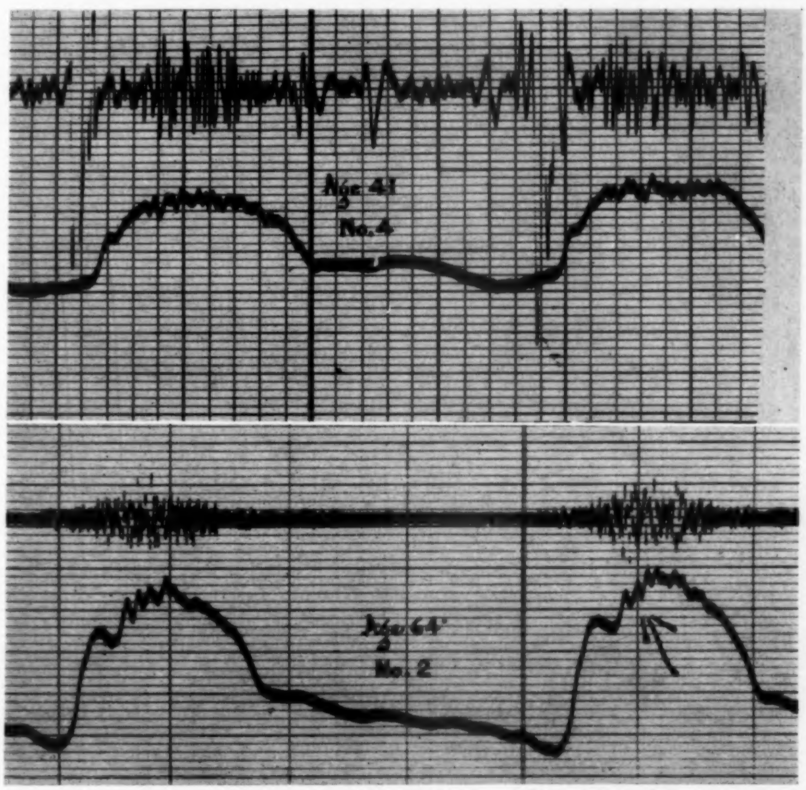

Fig. 3.—Pulse tracing of two cases of calcific aortic stenosis showing characteristic systolic vibrations. The phonocardiogram in the upper tracing was taken at the apex (Cases 4 and 2).

A 71-year-old man (Case 10) was the only patient in whom the carotid pulse showed no systolic vibrations. He died from metastatic carcinoma within the year following the study. At postmortem examination the aortic leaflets were heavily calcified and appeared like two rigid shelves. The valve orifice was narrow and slit-like. It is possible that the extreme rigidity of the aortic cusps with calcific buttressing may have produced vibrations of higher frequency than those from the usual stenotic orifice. It is noteworthy that the systolic murmur in this case was high-pitched and showed a double crescent in the phonocardiogram. This patient's carotid pulse and phonocardiogram are shown in Fig. 5.

Table I. Summary of Findings in the Patients of Group I

PATIENT	AGE, SEX	B.P. (MM.Hg)	SYSTOLIC MURMUR†		THRILL	A_1	A_2	HEART SIZE	ASSOCIATED LESIONS	FUNCTIONAL STATUS‡	PHONO-CARDIO-GRAM	CAROTID PULSE TRACING
			BASE	APEX								
1. J.J.	57, M	120/66	III	II	+	Absent	Diminished	Slight enlargement	A.R.	I	—	+
2. T.G.	64, M	140/50	IV	III	+	Absent	Absent	Slight enlargement	A.R.§	I	±	+
3. P.S.*	56, M	130/90	III	II	+	Normal	Absent	Slight enlargement	Pulmonary emphysema	II	±	+
4. M.D.*	41, M	110/80	IV	III	+	Absent	Very much diminished	Moderate enlargement	A.R., M.S.	II-III	±	+
5. A.S.	78, M	150/100	II	II-III	0	Absent	Normal	No enlargement	Cancer, advanced	I	—	+
6. P.N.	45, M	170/80	V	II-III	+	Absent	Very much diminished	Moderate enlargement	A.R.	I	+	+
7. W.F.	54, M	140/100	IV	II-III	+	Very much diminished	Very much diminished	No enlargement	A.R.	II	±	+
8. C.W.	57, M	110/88	III	I-II	0	Normal	Normal	Slight enlargement	A.R.	II	—	+
9. A.C.**	62, F	120/76	IV	IV	+	Absent	Diminished	Slight enlargement	Myocardial infarction	II-III	—	+
10. A.M.*	71, M	120/60	III	IV	+	Absent	Very much diminished	Slight enlargement	Cancer, advanced	I	+	—
11. E.L.**	80, M	160/100	II-III	I-II	+	Absent	Diminished	Moderate enlargement	None	II-III	+	+
12. E.L.*	29, M	100/60	III	III	+	Absent	Normal	Marked enlargement	M.R.-A.R., M.S.	II	—	+
13. M.H.	72, F	150/90	II	II	0	Very much diminished	Very much diminished	No enlargement	Thyrocardiac	II	—	+

14. A.B.*	61, M	128/70	IV	II-III	0	Absent	Diminished	Slight enlargement	M.S.	III	±	+
15. P.K.	61, M	180/110	II	II	0	Diminished	Normal	Moderate enlargement	Hypertension, Paget's disease	II-III	±	+
16. O.C.**	58, M	100/74	I	I	0	Absent	Absent	No enlargement	Myocardial infarction, emphysema	III	−	+
17. R.R.	42, M	110/66	IV	III	+	Absent	Absent	Slight enlargement	A.R.	I	+	+
18. R.W.	37, M	140/30	IV	IV	+	Absent	Very much diminished	Moderate enlargement	A.R.§	I	+	+
19. I.T.*	54, F	106/55	III	IV	+	Absent	Normal	Marked enlargement	A.R.§	II	−	+
20. W.G.	53, M	130/70	III	II	0	Very much diminished	Very much diminished	Moderate enlargement	None	II	−	+
21. E.K.	62, M	150/85	II	II	0	Absent	Absent	Moderate enlargement	Emphysema	I	−	+
22. T.W.*	77, F	135/70	III	II	0	Absent	Absent	Slight enlargement	None	II-III	±	+
23. M.S.**	73, F	160/80	V	IV	+	Absent	Absent	Moderate enlargement	Hypoalbuminemia	II-III	+	+
24. J.H.	86, M	118/60	II-III	II	0	Very much diminished	Very much diminished	Moderate enlargement	A.R.	II-III	−	+
25. J.C.	51, M	120/84	IV	III	+	Absent	Absent	Moderate enlargement	A.R.	I	+	+

*Died, and postmortem done.
**Died, and postmortem not done.
†In accordance with Dr. S. A. Levine's classification, Grades I-VI.
‡According to the New York Heart Association classification.
§Hemodynamically significant aortic insufficiency.
A.R.: Aortic regurgitation. M.S.: Mitral stenosis. M.R.: Mitral regurgitation.
Phonocardiogram: − No diamond shape. ± Variable diamond shape. + Diamond shape.

Later in the study we encountered a case similar to the one just described. A 73-year-old woman (Case 23) had the clinical findings of aortic stenosis, but the systolic vibrations were absent in the pulse tracings. The systolic murmur was very high-pitched, as in Case 10, and suggested that the absence of the characteristic pulse contour might be due to the recording system. Therefore, to raise the frequency response, the tubing was shortened and, by applying the cup tightly, very fine systolic vibrations were recorded from both carotid arteries (Fig. 6). This further emphasized the importance of "tuning in" by adjusting the frequency response of the recorder.

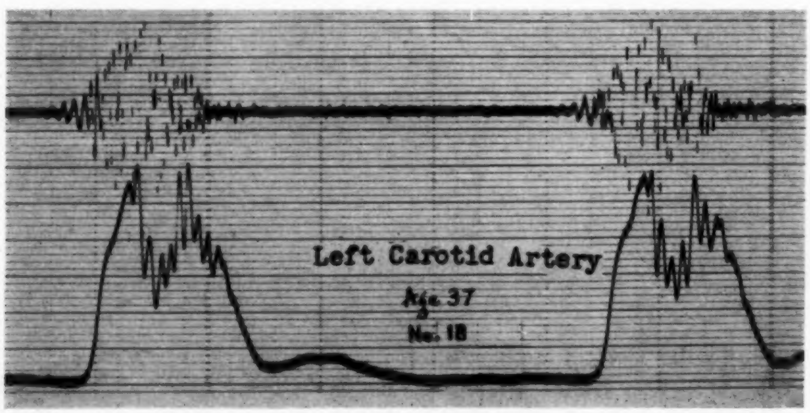

Fig. 4.—Pulse tracing of a 37-year-old man (Case 18) with calcific aortic stenosis and significant aortic insufficiency. The diastolic murmur of aortic regurgitation is not apparent on the phonocardiogram taken with open bell and stethoscopic amplifier.

A comparison between a direct intra-arterial recording at a speed of 25 mm. per second of the brachial artery pulse and an indirect carotid pulse tracing is shown in Fig. 7 (Case 17). The systolic vibrations (slightly exaggerated by the faster paper speed of 75 mm. per second) are clearly visible in the carotid tracing, but are not present in the intra-arterial recording. Their absence in the latter is most likely due to attenuation of the high-frequency vibrations by the column of blood.

Group II: Aortic Stenosis Without Leaflet Calcification.—Of the 45 individuals in Group II, there were 23 (Subgroup A) with no clinical evidence of mitral valvular involvement or hemodynamically significant aortic regurgitation. There were 9 females and 14 males in the group of 23. Their ages ranged from 5 to 84 years, the average age being less than that in Group I. A systolic basal thrill was present in 18 of the 23. The aortic first sound was recorded by phonocardiography with greater frequency than in Group I. All 23 patients showed systolic vibrations in the carotid pulse tracings. The rest of the clinical findings were not essentially different from those in Group I and therefore are not described here. There have been no deaths in Subgroup A.

The remaining 22 of the 45 patients in Group II (Subgroup B) had mitral stenosis as well as aortic stenosis. There were 18 females and 4 males, ranging

in age from 28 to 50 years, with the majority under the age of 40. In 10 patients the systolic murmur at the apex was equal to or louder than that at the aortic area. A systolic basal thrill was present in 12. In most of the 22 patients the mitral stenosis was judged to be the predominant lesion.

The characteristic systolic vibrations in the carotid pulse were recorded in 21 of the 22 patients in Subgroup B. In 2 patients the aortic systolic murmur was only Grade I to II in intensity, and aortic stenosis was not suspected until after the positive carotid pulse contour had been obtained. In one of these patients, aortic stenosis was subsequently verified at surgery, whereas in the other no definitive diagnostic or surgical procedure has been carried out.

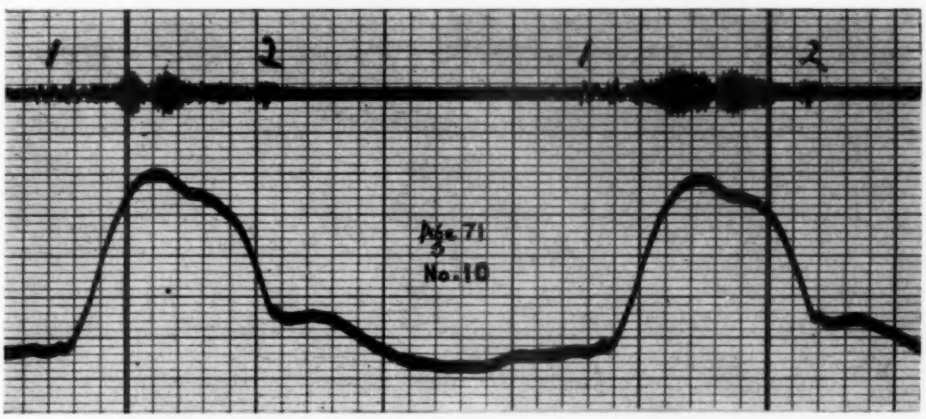

Fig. 5.—Pulse tracing of a 71-year-old man (Case 10) showing absence of systolic vibrations. Note the double crescent-shaped murmur. Discussion in text.

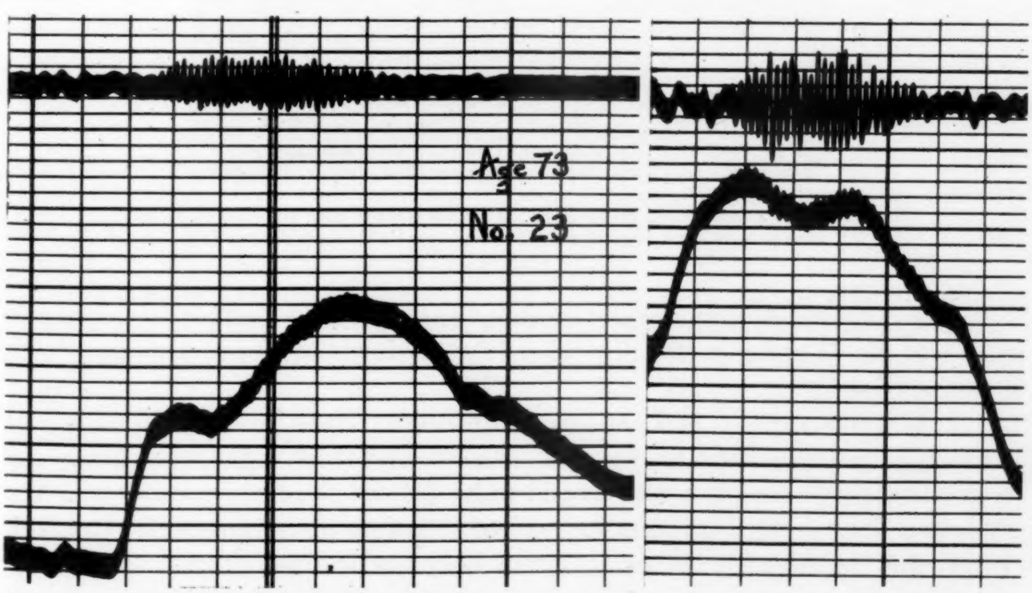

Fig. 6.—Pulse tracing of a 73-year-old woman (Case 23) with calcific aortic stenosis. The photographs are enlarged to show extremely fine high-frequency vibration.

The patient in whom the systolic vibrations were absent was a 34-year-old woman with clear-cut mitral stenosis; aortic stenosis was strongly suspected because of a Grade II systolic murmur limited to the aortic area. However, on several attempts, the carotid pulse tracing failed to show the typical changes. Aortic stenosis and mitral stenosis were demonstrated subsequently at autopsy. She was the only patient in this group of 22 who did not have the characteristic carotid pulse contour. In the 2 additional patients who died, postmortem examination was not done.

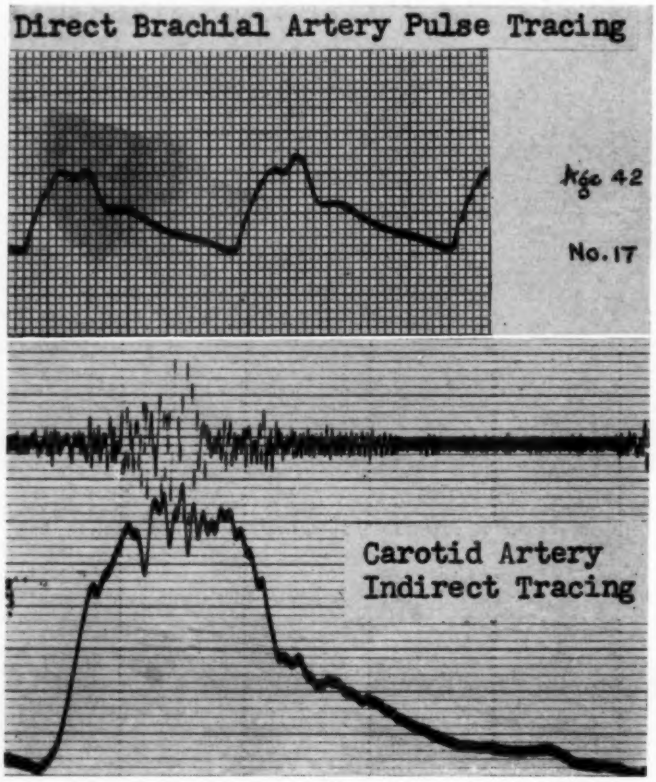

Fig. 7.—Comparison of the direct brachial artery tracing with the indirect carotid artery tracing in a patient with calcific aortic stenosis (Case 17).

The diamond-shaped systolic murmur was seen in the phonocardiogram in only 4 of the 22 patients, the 4 in whom the predominant lesion appeared to be aortic stenosis.

It is of interest that in 3 patients, not included in this study, who had severe aortic regurgitation and a loud systolic murmur and thrill at the base (functional or relative aortic stenosis), the carotid pulse did not show the contour of aortic stenosis. One of these patients succumbed following placement of the Hufnagle valve, and at postmortem examination only aortic regurgitation and mitral stenosis were found, with no anatomic stenosis of the aortic valve. Anatomic confirmation in the other 2 patients is as yet not available.

DISCUSSION

Our observations in these 70 patients confirm the clinical findings of others.[1,2] A narrow pulse pressure is infrequent in aortic stenosis. The systolic murmur at the apex may be as loud as, or louder than, that at the base in the absence of mitral regurgitation or significant left ventricular enlargement, or both. A systolic thrill at the base is an inconstant finding and, in fact, was absent in 25 (30 per cent) of the 70 patients. It is apparent that even severe isolated aortic stenosis, as seen in a number of our patients at postmortem examination, is found in the elderly with minimal or no incapacity during life.

Special attention was paid to the presence of a diamond-shaped murmur in the patients of Group I and Subgroup B of Group II. In the former it was recorded phonocardiographically in 14 of the 25, but was consistently present in the same recording in only 7 of the 14. In patients with atrial fibrillation the murmur was diamond-shaped only after the longer R-R intervals. In Subgroup B the diamond-shaped murmur was seen in only 4 of the 22 patients, the 4 in whom the predominant lesion appeared to be aortic stenosis.

A recording of the carotid pulse by the indirect method described here is a definite aid in the diagnosis of aortic stenosis. It should be noted that the method provides only qualitative information. The advantages over an intra-arterial recording of the brachial pulse include simplicity, avoidance of arterial puncture, proximity to the central pulse source, and a tuned frequency response. The importance of the latter was illustrated by Case 23, in which systolic vibrations were recorded only after raising the frequency response of the system.

From our experience in this study, we doubt that a delay in ascent of the carotid pulse, i.e., slope time, is of definitive value in the qualitative or quantitative diagnosis of aortic stenosis as suggested by Duchosal and associates.[19] We have encountered a marked delay in slope time in normal elderly people and in patients with myocardial failure. The delay seems to be associated as much with myocardial function as with aortic stenosis. The use of slope time would have more value in these studies if indirect methods could provide a frequency response which is flat to direct current (zero cycles per second) in order to avoid phase distortion. The nonlinear low-frequency systems employed at the present time tend to distort the ascent of the pulse contour, thus invalidating this approach.

The observation that absence of the dicrotic notch in the subclavian and radial pulse contours indicates valvular rather than subaortic stenosis[12] is not borne out by our study. The majority of our patients with valvular aortic stenosis demonstrated a well-defined dicrotic notch. It is possible that this discrepancy is due to the difference in the recording systems as well as the different peripheral artery used.

SUMMARY

The clinical findings in 70 individuals with aortic stenosis are reported. Confirmation of the diagnosis was available in 28. Special emphasis was placed on the indirect recording of the carotid pulse as a diagnostic aid. By means of

a "tuned" system, the characteristic contour of aortic stenosis, consisting of a plateaued curve with systolic vibrations, was obtained in 68 of the 70 patients (97 per cent). It is felt that the method described offers a simple and practical diagnostic aid.

The authors wish to thank Dr. Clayton B. Ethridge for his editorial help.

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Critical Study of the Relationship Between Angina Pectoris and Coronary Atherosclerosis

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The clinical diagnosis of atherosclerosis is difficult in the living man, and in this difficulty lies an important obstacle to the statistical study of this disease. However, among the indirect evidences which may reveal the presence of atherosclerosis, angina pectoris (angina of effort) arouses special interest, since it is one of the main clinical expressions of coronary atherosclerosis. Its identification can usually be made accurately, and is infrequently mistaken.[1] The scope of this study is to assess the reliability of this symptom when used as a clinical criterion of coronary atherosclerosis.

MATERIAL AND METHODS

This survey is based on the analysis of 188 clinicopathologic records of cases of angina pectoris, complicated or not by anginal pain of long duration or by pain occurring at rest. These records were extracted from a series of 828 autopsies of cardiac patients, performed in the Department of Cardiology, Hôpital Boucicaut, Paris, during the period 1949-1957

1. *Coronary atherosclerosis* was considered significant when it reduced by at least 50 per cent the coronary arterial tree, or when it occluded at least one of the three important coronary trunks. Other conditions liable to affect the heart (syphilitic aortitis, arterial hypertension, valvular disease, chronic lung or bronchial disease, auricular fibrillation) might or might not be associated.

2. *Angina pectoris* was considered present when attacks of pain of short duration (generally 1 to 3 minutes, always less than 15 minutes) occurred, intimately related to effort and almost always to walking. As a matter of fact, even when one is most careful to eliminate the right upper quadrant abdominal pain secondary to failure of the right ventricle,[2,3] all of the types of pain coming under this definition do not carry with the same strength the idea of angina pectoris. This is the reason that our 188 observations were divided into two groups: typical angina pectoris and atypical angina pectoris.

Typical angina pectoris: In 160 of the 188 cases (85 per cent) angina pectoris was obvious. It consisted of pain of a burning or constricting character, its site being generally retrosternal, less often laterosternal, brachial or epigastric, was provoked by walking, compelling the patient to stop, and then disappeared within 1 to 5 minutes. These attacks, although variable in occurence, are customary enough to be recognized as genuine.

Atypical angina pectoris: In 28 of the 188 cases (15 per cent) angina pectoris was either suspected or questionable, but not absolutely definite. In some cases it consisted of vague sensations

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Received for publication May 28, 1959.

occurring on effort other than walking, and only compelled the person to slow down. In other cases the attacks occurred once or twice, or lasted for as long as 10 to 15 minutes. Finally, in rare cases the pain resembled the abdominal pain secondary to failure of the right ventricle.

RESULTS

In order to test how reliably angina pectoris reflected coronary atherosclerosis, the 188 cases were divided into different clinical groups, each group being subsequently correlated with the pathologic findings (Fig. 1).

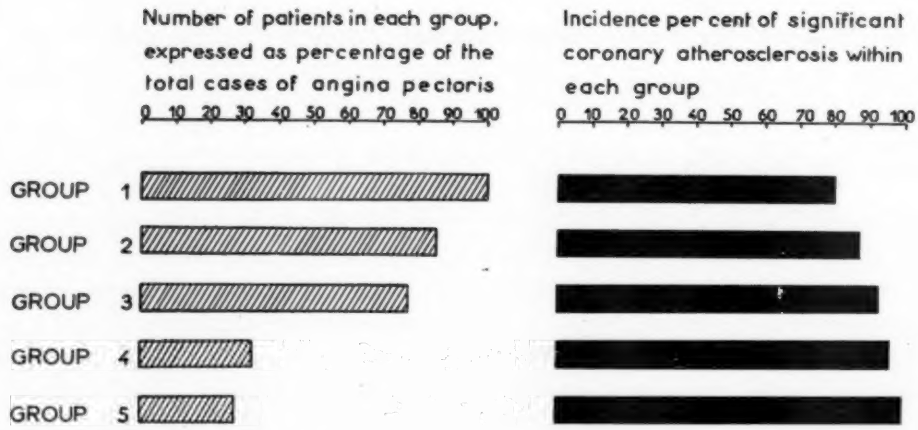

Fig. 1.—Relationship of angina pectoris and coronary atherosclerosis in different clinical groups. *Group 1:* Unselected cases of angina pectoris. *Group 2:* Typical angina pectoris. *Group 3:* Angina pectoris with or without arterial hypertension (excluding cases associated with syphilitic aortitis, valvular disease, chronic cor pulmonale, auricular fibrillation). *Group 4:* Primary, isolated angina pectoris (excluding hypertensive cases). *Group 5:* Typical and primary angina pectoris.

Group 1.—There was no selection whatsoever in this group; it included all of the 188 cases. Significant atherosclerosis was found in 151 of the 188 cases (80.3 per cent), among which 61 cases had occlusion of all three coronary trunks, 45 cases had occlusion of two trunks, 35 had occlusion of one trunk, and 10 cases had tight stenoses of all three trunks.

Group 2.—Out of the 188 cases observed, there were 160 (85 per cent) in which the symptom of angina pectoris was absolutely typical, therefore leaving 28 cases in which the symptom was only suspicious. Significant atherosclerosis was found in 139 of these 160 cases (86.8 per cent), including 59 of the 61 cases having occlusion of all three trunks (96.6 per cent), 42 of the 45 cases with occlusion of two trunks (93.3 per cent), 31 of the 35 cases with occlusion of one trunk (88.5 per cent), and 7 of the 10 cases with tight stenoses of the three trunks (70 per cent).

Group 3.—Out of the 188 cases observed, 146 (77 per cent) remained after the cases of angina pectoris associated with other factors of heart disease (syphilitic aortitis, valvular disease, chronic lung and bronchial disease, auricular fibrillation), excepting hypertension, had been discarded. Significant atherosclerosis was found in 136 of the 146 cases in this group (93 per cent).

Group 4.—Out of the 188 cases observed, 60 (32 per cent) remained in this group after eliminating from Group 3 the cases associated with arterial hypertension. Significant atherosclerosis was found in 58 of the 60 cases in this group (96 per cent).

Group 5.—Out of the 188 cases observed, 52 (27 per cent) were included in this group after discarding the clinically atypical cases, the secondary ones, and those associated with other heart diseases. Significant atherosclerosis was found in all of the 52 cases of this group (100 per cent).

COMMENTS

Although this survey was based on the autopsy records of the cardiological department of a general hospital, we believe that these findings may be used for a biological study of atherosclerosis in the living man, for the following reasons.

1. *The coronary lesions* found in anginal patients who died accidentally of noncardiac causes differ little, in nature and in degree, from those found in patients dying of their coronary trouble.[4]

2. *The sampling offered* by these 828 autopsies seems to be fairly representative of the causes of heart disease in general. Among the 1,009 etiological factors found in these 828 records, 271 consisted of rheumatism (32 per cent), 259 of coronary atherosclerosis (31 per cent), 246 of arterial hypertension (29 per cent), and 233 of miscellaneous causes (28 per cent).

3. *The pathologic criteria of coronary atherosclerosis* which were used were particularly severe ones, since the presence of occlusive and/or stenosing atherosclerosis was required in order for the condition to be considered as significant. In many cases, however, coronary atherosclerosis, although evident and important, was not found significant enough to be taken into consideration, and those cases were therefore discarded.

These clinicopathologic correlations establish both the value and the limits of the symptom "angina pectoris" (angina of effort), when used as a criterion to detect the presence of coronary atherosclerosis. But, they also demonstrate the necessity of a preliminary selection of the cases for study, because: (1) Coronary atherosclerosis dominates the etiology of angina pectoris so much that in our group of unselected anginal patients (Group 1) significant atherosclerosis was found in 80.3 per cent. (2) However, to obtain greater accuracy in the identification of coronary atherosclerosis, it is necessary to select the observations. In our 188 cases, Group 2 (typical angina pectoris) and Group 3 (angina pectoris with or without hypertension, but exclusive of all other etiological factors) represent, respectively, 85 and 77 per cent of our original material, and contain, respectively, 87 and 93 per cent of the cases of coronary atherosclerosis. Group 4 (primary anginal cases) and Group 5 (primary anginal cases, clinically typical) represent, respectively, 96 and 100 per cent of the cases of significant atherosclerosis, but only 32 and 27 per cent, respectively, of the original 188 cases.

Although in selected cases the presence of angina pectoris (angina of effort) is an almost perfect evidence of underlying coronary atherosclerosis, since it was found in 100 per cent of the cases of our Group 5 (typical and primary cases),

they do not coincide absolutely with each other, because in many cases in which significant atherosclerosis was discovered at autopsy the patient never complained of this symptom during life. In our material of 828 autopsies of cardiac patients, 640 patients never had during life any suggestion of angina pectoris, and yet, significant atherosclerosis was found in 108 of them (16.8 per cent). This fact shows quite clearly the limits of this symptom as a discriminative criterion.

SUMMARY AND CONCLUSIONS

Angina pectoris (angina of effort) is a symptom which can be accurately identified, except in a minimal number of cases, and which also offers very valuable indirect evidences, in the living subject, of underlying coronary atherosclerosis. Significant atherosclerosis, i. e., stenosing and/or occlusive, is indeed present in: 80 per cent of unselected cases of angina pectoris; 87 per cent of cases of clinically typical angina pectoris; 93 per cent of cases of angina pectoris when cases with etiological factors other than hypertension are excluded; 96 per cent of cases of isolated angina pectoris, excluding the cases with hypertension; and 100 per cent of the cases that show a clinically typical and isolated angina pectoris.

These evaluations may be of some help in selecting subjects for the purpose of biological or statistical studies on coronary atherosclerosis.

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Clinical Analysis of Right Bundle Branch Block

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In the fields of clinical medicine, established criteria need constant re-evaluation. It may be stated that the prognostic significance of any form of bundle branch block rests on the nature of the underlying pathologic entity involving the heart, and it may be further stated that once the nature of the heart disease is known, there is no prognostic significance to the presence of bundle branch block. However, the finding of bundle branch block in routine electrocardiograms, not accompanied by clinical symptomatology and x-ray findings, puzzles the physician and confronts him with the question of the prognostic significance of the electrocardiographic finding. In the search for an answer to this question and in order to re-evaluate previously established dicta, it was decided to analyze all cases of bundle branch block recorded in the electrocardiographic files of Gorgas Hospital in the years 1952 through 1958. This first paper deals with complete right bundle branch block.

CRITERIA FOR DIAGNOSIS

The criteria for the diagnosis of complete right bundle branch block have changed little since originally set forth by Wilson, in 1931. The duration of the QRS complex must be 0.12 second or greater, as measured in the chest leads of a twelve-lead electrocardiographic tracing. While the rSR or rR′ patterns are usually seen in Leads V_1-V_2 and aV_R, together with a broad S in Lead I and secondary ST-T wave changes in these leads, they are secondary criteria establishing the site rather than the extent of the block, and are subject to positional variations.

Most often the diagnosis of complete right bundle branch block is not made until the time of electrocardiography; however, it may be suspected in cases which have splitting of either the first or second heart sounds. The absence of a characteristic mean vector or QRS loop is reported by both Sodi-Pallares and Lasser, leaving the diagnosis in the realm of "pattern" or standard electrocardiography.

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Received for publication June 1, 1959.

MECHANISM OF PRODUCTION

The electrocardiographic tracing of complete right bundle branch block is produced when the duration of the electrical activity of depolarization of the combined ventricular muscle mass exceeds 0.12 second and the terminal vectors are directed toward the right. The separate investigations of Sodi-Pallares and Dickens and Goldberg, using intracardiac and epicardial electrodes, have demonstrated this electrical pattern to be the result of two-phase septal depolarization. The upper septum is depolarized as usual, but there is a delay in the depolarization of the lower septum, which occurs terminally, resulting in a terminal vector directed to the right, with an R′ in Leads V_1, V_{3R}, and aV_R. The ST-T changes are of the secondary rather than the primary type, except in cases of coronary vascular disease.

CASE PRESENTATIONS

The population represented in these studies is composed of three groups: (1) Panamanian nationals and their dependents, (2) U. S. civil service employees and their dependents, and (3) U. S. military personnel and their dependents. The first two of these three groups are comparable to a cross-section of an average American community. The third group contains an abnormally high number of young healthy males, which may, in some degree, affect the following figures.

In the 7-year period from January, 1952, through December, 1958, there were 17,750 twelve-lead electrocardiograms taken in Gorgas Hospital. These examinations represent 8,770 individuals, because our re-examination rate is 50 per cent. In these tracings there were 179 instances of complete right bundle branch block, representing 100 separate cases. This produces an incidence of 1.15 per cent or a prevalence of 11.5 per 1,000 patients examined.

Our 100 cases of right bundle branch block are tabulated in Table I according to disease process, age at the time of discovery, and sex. Summarizing Table I, we can say that in 62 per cent of our cases of complete right bundle branch block there was evidence of heart disease, of which arteriosclerotic heart disease was the most prevalent. It is interesting to note that there is a 3:1 prevalence of males in our group in which no heart disease was found; however, the prevalence of males is reduced to 2:1 in the group with diagnosed heart disease.

There were 23 fatalities in the 100 cases of right bundle branch block recorded in this 7-year period. These fatalities are tabulated in Table II. In the three cases in which there was no heart disease the deaths were due to carcinoma of the lung, pulmonary tuberculosis, and amyotrophic lateral sclerosis.

DISCUSSION AND CONCLUSIONS

In an attempt to verify the frequently heard statement that right bundle branch block is often of little clinical significance, we have collected the aforementioned material. Our findings are basically in agreement with those of Bayley, who reported that in 24 per cent of his cases there was no evidence of heart disease. While we find that in one out of three of our cases of right bundle branch

block there is no heart disease, the probability is that if these persons were properly followed up and investigated, many would be diagnosed as having some form of cardiac abnormality. Table II further demonstrates that the coincidence of right bundle branch block and diagnosed heart disease indicate a poorer prognosis than does right bundle branch block alone. Twenty subjects out of a group of 62 died when right bundle branch block and heart disease were present, but only 3 out of 38 who had right bundle branch block died when no heart disease was diagnosed.

TABLE I

TYPE OF CARDIAC DISEASE	TOTAL CASES	MALE	FEMALE	AVERAGE AGE (YR.)
Hypertensive cardiovascular disease	22	14	8	61
Arteriosclerosis	30	22	8	67
Rheumatic heart disease	5	3	2	33
Congenital heart disease	2	0	2	18
Heart disease of unknown etiology	3	1	2	30
Total with heart disease	62	40	22	58
No heart disease	38	29	9	56
Grand total	100	69	31	—

TABLE II

DISEASE	TOTAL CASES	DEATHS			TOTAL DEATHS	PER CENT
		0-1 MO.	1-12 MO.	12-48 MO.		
Hypertension	22	–	1	5	6	27
Arteriosclerosis	30	4*	4	3	11	37
Rheumatic heart disease	5	–	3	–	3	40
Congenital heart disease	2	–	–	–	0	—
Undiagnosed heart disease	3	–	–	–	0	—
Total with heart disease	62	4	8	8	20	32
No heart disease	38	–	–	–	3	7.8
Grand total	100	–	–	–	23	23

*All of these were due to acute myocardial infarction.

The interesting predominance of this condition in males, as compared to females, has led us to re-examine our cases and the population from which we have obtained the tracings. Although at first the presence of a military segment in our population might seem to explain this finding, the average age of our subjects is far above the usual retirement age of military personnel and probably is not grossly affected by this group. Another point of potential error is due to the fact that a number of our tracings are taken as annual physical examinations and pre-employment examinations, in both of which instances males predominate;

however, this would fail to explain the prevalence in those subjects with heart disease, since they, in general, fall outside these groups of pre-employment and young military personnel.

SUMMARY

1. Complete right bundle branch block is associated with heart disease in 62 per cent of our cases.

2. Arteriosclerotic heart disease is the most common variety of heart disease associated with right bundle branch block.

3. The prognosis for right bundle branch block is considerably more grave when associated with diagnosed heart disease.

4. There is an unexplained predominance of males in both the group with and the group without detectable heart disease.

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Ruptured Abdominal Aortic Aneurysm With Massive Gastrointestinal Hemorrhage

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Rupture of an abdominal aortic aneurysm associated with gastrointestinal hemorrhage is extremely uncommon. The first case of an aneurysm that ruptured through the duodenum into the gastrointestinal tract was reported by Salmon, in 1843. In 1943, Rottino[1] collected 31 cases from the literature and added one of his own. Hunt and Weller,[2] in 1946, added 9 cases from the literature including one of their own. Since 1946, an additional 22 cases have been reported, making a total of 63 cases.

One of these was the case recorded by Voyle and Moretz,[3] in 1958, in which for the first time an attempt was made at surgical resection of the ruptured aneurysm and replacement with an arterial homograft; however, the patient expired on the thirty-seventh postoperative day, with the clinical signs of a left cerebrovascular accident.

This report presents 4 cases of abdominal aortic aneurysm with massive gastrointestinal hemorrhage, in three of which the rupture occurred directly into the third portion of the duodenum, and in the fourth case the rupture was into the intra- and retroperitoneal spaces, but there was no demonstrable communication between the lumen of the intestine and the aneurysm at autopsy.

CASE REPORTS

CASE 1.—L. T., a 69-year-old white man, entered St. Joseph's Hospital on Oct. 17, 1958, with the complaint of sudden onset of severe substernal pain. The patient had a similar episode in February, 1958, which was relieved by nitroglycerin. He did well until 12 days following admission, when he had moderate abdominal pain and extreme weakness followed by hematemesis and melena. An upper gastrointestinal series was performed but disclosed no source of bleeding. At that time the radiologist suggested the possibility of an abdominal aortic aneurysm because of the presence of a crescent-shaped calcification in the left hemiabdomen (Fig. 1). Barium enema and proctosigmoidoscopic examinations failed to disclose the origin of the hemorrhage. The bleeding lasted for 2 days; the patient was transfused and dismissed from the hospital on Nov. 7, 1958.

The patient was readmitted on Dec. 1, 1958, in a state of shock, with the history of having passed a large amount of tarry stool associated with abdominal pain beginning early that morning.

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Received for publication June 12, 1959.

Physical examination revealed the patient to be well developed and well nourished, but in acute distress. The skin was pale and clammy. The blood pressure was 60/0 mm. Hg. Pulse was 120 per minute and weak. The lungs were clear. The cardiac rhythm was regular. The abdomen was moderately distended and markedly tender in the left lower quadrant. No masses were palpated. Pertinent laboratory data included a hemoglobin of 5.8 Gm., and a negative blood serology. The patient began vomiting blood and expired 12 hours after admission.

At autopsy, the heart weighed 450 grams and showed a marked, diffuse coronary arteriosclerosis with an old occlusion of the descending branch of the left coronary artery. The anterior portion of the interventricular septum was extensively fibrosed. The lungs were markedly congested and edematous.

Fig. 1.—Case 1. Radiograph of the abdomen, showing enlargement of the aorta and a crescent-shaped line of calcification.

The esophagus was slightly dilated and filled with a coffee-grounds type of material. More than 1,000 c.c. of clotted blood was found in the markedly distended stomach. The entire small and large intestine contained approximately 1,000 c.c. of a dark, bloody fluid.

The third portion of the duodenum was lifted forward by a fusiform type of aneurysm measuring 6 by 5 cm., beginning about 2 cm. below the renal arteries and terminating 3 cm. above the bifurcation of the aorta. The aneurysm was found to be densely adherent to the posterior aspect of the duodenum (Fig. 2). A rounded perforation measuring 1 cm. in diameter was present in the third portion of the duodenum, communicating with the abdominal aneurysm (Fig. 3). The aneurysm was filled with clotted blood. The wall was 2.5 cm. thick, with laminated, organized mural thrombi.

Microscopic examination of the site of the perforation showed an extensive area of acute inflammatory reaction throughout all layers of the duodenum, with hemorrhage and necrosis. The aorta showed marked arteriosclerotic changes with calcification and areas of bone formation.

Case 2.—W. R., an 81-year-old white man, was brought by ambulance to the Bryan Memorial Hospital on Jan. 4, 1959, with the complaint of severe abdominal pain, rectal bleeding, weakness, and dizziness. The patient had been having abdominal pain, which was most severe in the lower abdomen, for the past 3 weeks. For a period of about 1 month his appetite had been very poor. He had had dizzy spells for several days prior to admission.

On admission the patient appeared pale and in a semishock condition. The blood pressure was 60 mm. Hg. Pulse was 104 per minute and very weak. The abdomen was slightly distended. No masses were palpated. Rectal examination revealed tarry stools. Laboratory data included a hemoglobin of 9.0 Gm., and a negative blood serology. The patient required multiple transfusions to maintain his blood pressure above 100 mm. Hg. During the course of hospitalization he constantly complained of abdominal pain and had several episodes of bloody stools.

Exploratory laparotomy was scheduled for the fourth hospital day, but the night prior to surgery he developed sudden dyspnea and expired.

At autopsy, the stomach was markedly dilated and contained approximately 1,500 c.c. of bloody fluid and large masses of blood clots. In the posterior aspect of the third portion of the

Fig. 2.

Fig. 3.

Fig. 2.—Case 1, specimen. The aorta (*A*) and the aneurysm (*B*) are markedly adherent to the third portion of the duodenum (*C*). The actual point of perforation is not shown.

Fig. 3.—Case 1, specimen. Notice the ragged perforation in the duodenum.

duodenum there was a defect in the wall, measuring up to 2.5 cm. in diameter. There was a large, friable, gray-white-to-pink, hemorrhagic mass protruding through, and loosely adherent to, the margin of this defect (Fig. 4). This defect was in communication with an underlying saccular aneurysm measuring 4 cm. in diameter. The entire small and large intestine contained approximately 800 c.c. of bloody fluid.

Microscopic section of the aorta in the region of the aneurysm revealed the presence of only a few medial elastic fibers in some zones. An extremely thick, laminated thrombus was adherent to the inner aspect. In some areas there was extensive intimal atherosclerosis with heavy cholesterol, lipid, and calcium deposits. In the region of the perforation there was evidence of recent and old hemorrhage, with intense infiltration of leukocytes in the adventitia and surrounding tissues.

Fig. 4.—Case 2, specimen. The third portion of the duodenum shows a large ragged perforation with a very hemorrhagic base.

Case 3.—J. N., a 75-year-old white man, was first admitted to the Lincoln General Hospital on May 23, 1949, with the chief complaint of a pulsating mass in the upper abdomen, which had been present for several months prior to admission. Physical examination revealed a firm, semifixed, pulsating, globular mass and slight tenderness in the epigastric region. The blood pressure was 154/84 mm. Hg. Pulse was 80 per minute. Respiration was 20 per minute. Laboratory data showed a red bood cell count of 3.8 million, with a hemoglobin of 11.3 Gm.

On May 27, 1949, the abdomen was explored and found to contain a large aortic aneurysm. A Harrington's operation was performed using the fascia lata. The postoperative course was uneventful, and the patient was dismissed 2 weeks after surgery.

The patient was readmitted on Oct. 17, 1951, in profound shock, with a history of weakness, syncope, and hematemesis. The blood pressure was 78/0 mm. Hg. Pulse was 116 per minute. Respiration was 26 per minute. A large pulsating mass was present in the mid-upper abdomen. Laboratory data showed a hemoglobin of 7.1 Gm., and a red blood cell count of 2.6 million.

The patient's condition gradually improved with conservative treatment, including transfusion of 5 units of blood. He was discharged on Oct. 26, 1951, with a diagnosis of gastrointestinal hemorrhage due to a perforated abdominal aortic aneurysm. The patient was readmitted the following day because of the passage of a tarry stool associated with nausea and fullness of the abdomen. The blood pressure was 84/66 mm. Hg. Pulse was 88 per minute and weak. The

patient was conscious but markedly pale. He continued to have upper abdominal pain and tarry stools. In spite of blood and fluid transfusions, he gradually became comatose and expired on the fourth day after admission.

Autopsy revealed the stomach to be distended with approximately 500 c.c. of clotted blood. The entire small and large intestine were filled with 900 c.c. of tarry stool. The second and third portions of the duodenum had been displaced anteriorly and superiorly by the densely adherent aneurysmal mass, which measured 9 by 5 cm. and extended from the renal artery down to the bifurcation of the aorta.

Approximately 4 cm. proximal to the ligament of Treitz, there was a very narrow slit-like opening in the duodenal wall communicating with the aneurysm (Fig. 5). Microscopically, sections from the area adjacent to the perforation showed acute inflammation and necrosis of the duodenal wall. The aneurysmal wall revealed intimal and subintimal lipoid deposits, with destruction of the normal intima and replacement of the elastic media with laminated blood clots and fibrous connective tissue.

Fig. 5.—Case 3, specimen. Ragged narrow perforation in the third portion of duodenum.

Case 4.—C. H., a 61-year-old white man, was admitted to St. Joseph's Hospital on March 29, 1956, because of a mass in the abdomen which was discovered by the patient about 3 weeks prior to admission. The patient was a well-nourished, healthy appearing man in no distress. Physical examination revealed a hard, fixed, pulsating, nontender mass in the left upper abdomen. An abdominal aortogram was done on April 3, 1956, and suggested an extensive aneurysmal dilatation from the level of T_9 to L_2. Surgical intervention was thought inadvisable because of the extensiveness of the aneurysm. On Aug. 5, 1958, the patient was readmitted with complaints of intermittent abdominal pain, backache, and a steady increase in the size of the mass.

Severe abdominal pain began the night prior to admission and the patient passed approximately a quart of bright red bloody stool. On admission, physical examination revealed a large pulsating mass extending from the epigastrium to the left lower abdomen. Laboratory data revealed a hemoglobin of 12 Gm. and a negative blood serology. The patient continued to have bleeding per rectum. He suddenly had an epileptic seizure and expired about 7 hours after admission.

At autopsy, there was approximately 500 c.c. of bloody fluid in the free peritoneal cavity. There was a solid, fusiform type of aneurysm, measuring 16 by 14 by 5 cm., beginning just below the renal arteries and extending to the bifurcation of the internal and external iliac arteries bilaterally.

The rectosigmoid colon was fixed to the aneurysm by the markedly edematous and hemorrhagic mesocolon. The lumen of the aneurysm was filled with clotted blood. On the surface of the aneurysm and in the adjacent retroperitoneal space there was a large amount of clotted blood, but no communication could be demonstrated between the aneurysm and the retroperitoneal area nor between the aneurysm and the intestinal lumen. There was another saccular aneurysm measuring 5 cm. in diameter in the lateral wall of the lower portion of the thoracic aorta, 2.5 cm. above the diaphragm.

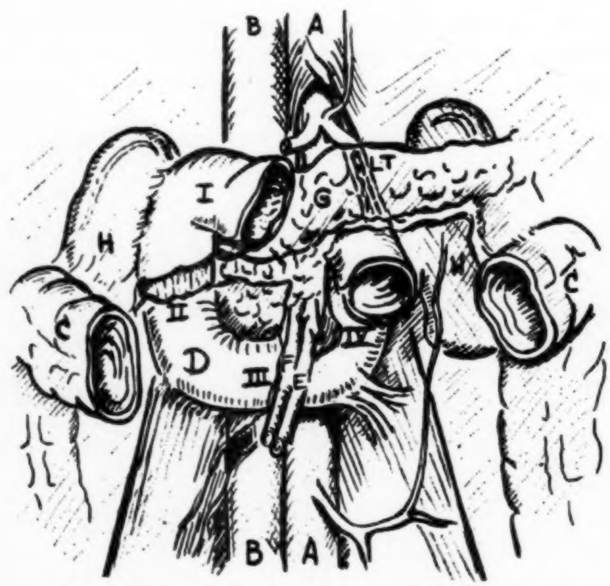

Fig. 6.—Diagram showing the anatomic relationships of the third portion of the duodenum (*DIII*) with the aorta (*A*), superior mesenteric vessels (*E,F*), ligament of Treitz (*LT*) and other structures. Inferior vena cava (*B*). Transverse colon (*C*). Pancreas (*G*). Kidneys (*H*).

DISCUSSION

With the declining incidence of syphilis and the increasing longevity of the population, arteriosclerotic aneurysms have become the most common type. They usually occur in the abdominal aorta below the origin of the renal arteries. According to the series of De Bakey,[4] only 3 out of 180 cases of abdominal aortic aneurysms extended above the renal arteries. They rarely develop before the age of 60 and are somewhat more common in males.

The occurrence of massive gastrointestinal hemorrhage caused by rupture of an abdominal aortic aneurysm is extremely rare. In a series of 14,900 autopsies at the Los Angeles General Hospital from 1941 to 1948, Hirst[5] found 7 cases of abdominal aortic aneurysms which ruptured into the duodenum. Morrison[6] reviewed 520 cases of aneurysms of the abdominal aorta reported prior to 1942, and found only 15 cases which had ruptured into the gastrointestinal tract. At present there are 67 recorded cases of abdominal aortic aneurysm which ruptured into the gastrointestinal tract, including the 4 cases in this presentation.

The most common site of rupture into the gastrointestinal tract was the duodenum (52 cases—81.3 per cent), particularly the third portion (44 cases—68.8 per cent). The reason for this high incidence of rupture into the third

portion of the duodenum is well explained by the combination of anatomicomechanical relations. The third portion of the duodenum is relatively fixed because of its retroperitoneal position, its relation to the superior mesenteric artery, ligament of Treitz, aortic wall, and the vertebral column (Figs. 6 and 7). Since these arteriosclerotic aneurysms of the lower abdominal aorta tend to bulge anteriorly over the course of time, these expansile pulsating masses can cause erosion, necrosis, and perforation of adjacent structures in much the same way as thoracic aneurysms do.

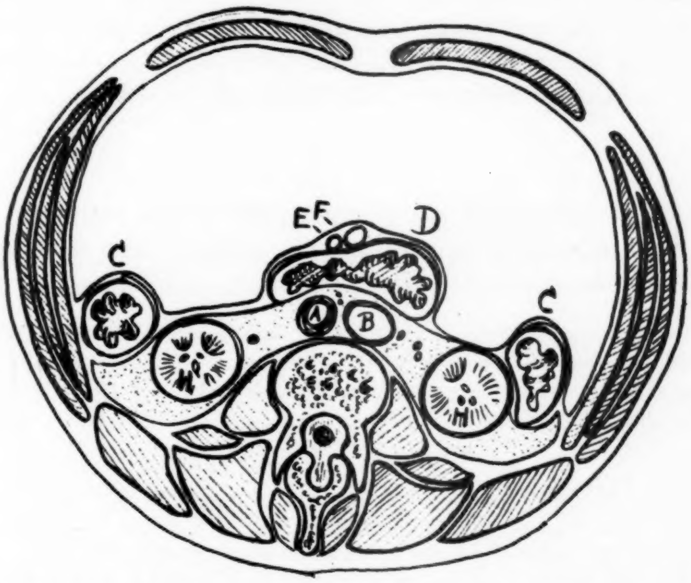

Fig. 7.—Diagram. Cross section of the abdomen at the level of the third portion of the duodenum. Notice the anatomic relationships of the various structures, labeled as in Fig. 6.

In Case 4, there was no evidence at autopsy of direct communication between the lumen of the intestine and the aortic aneurysm. A similar case was reported by Coggeshall and Genovese,[7] in 1950. They explained the gastrointestinal hemorrhage without direct communication with the intestine as being due to rupture of a large venous channel into the lumen of the intestine, secondary to obstruction of the venous return from the intestine by the massive hemorrhage in the mesentery. This seems a most reasonable explanation since in our fourth case the mesentery adjacent to the rectosigmoid was markedly distended with clotted blood.

According to De Bakey's series, the operative fatality rate for abdominal aortic aneurysm has rapidly declined from slightly over 20 per cent to less than 7 per cent (1956). The operative risk of perforated cases was more than 3 times that of the nonperforated cases. Also, the average period of survival after a diagnosis of abdominal aortic aneurysm is made is from 1 to 2 years, with rupture being the most common cause of death.

Attention is called to the fact that in a patient with a characteristic vascular crisis followed by gastrointestinal hemorrhage, in whom the history and findings

indicate the presence of an abdominal aneurysm which has been painful or tender, the possibility of perforation of the aneurysm into the gastrointestinal tract must be considered. Immediate definitive lifesaving measures, including surgical resection of the aneurysm and use of an arterial graft, should be carried out.

In our first case, surgical intervention should have been seriously considered after the first episode of hemorrhage, since the radiologist suggested the presence of an abdominal aortic aneurysm at the time.

In our fourth case, surgical exploration was withheld because of the questionable presence of an extensive thoraco-abdominal aneurysm, which turned out to be two separate aneurysms. However, surgery is the only lifesaving procedure even after the rupture of an aneurysm into the gastrointestinal tract, because this condition is uniformly fatal when left untreated.

SUMMARY

Four cases of abdominal aortic aneurysms which ruptured into the gastrointestinal tract with fatal hemorrhage are added to the series of 63 recorded cases. The incidence, etiology, and treatment are reviewed and briefly discussed.

We wish to express our appreciation to Dr. H. Papenfuss and Dr. M. Villaverde, of the Lincoln General Hospital, for permission to report two of the cases. We also extend our thanks to Dr. T. K. Lin, Cardiovascular Director, and Dr. H. Hopkins and Dr. J. Hession, of the Department of Medicine, for their cooperation.

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Pulmonary Schistosomatic Arteriovenous Fistulas Producing a New Cyanotic Syndrome in Manson's Schistosomiasis

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In cases of cor pulmonale due to Manson's schistosomiasis one of us (J.L.F.) has described arteriovenous aneurysms or arteriovenous fistulas originated by the action of schistosome eggs on pulmonary vessels.[10,11] These fistulas were observed also in two cases without cor pulmonale.[11] The clinical importance of such fistulas became evident in two cases of pulmonary schistosomiasis with marked cyanosis due to these fistulas.[13] A new and similar case diagnosed during life is to be reported now, and on the basis of these three cases a new cyanotic syndrome in pulmonary Manson's schistosomiasis is postulated.

CASE REPORT

The subject of this report is L. M. C., a 19-year-old colored (mulatto) Brazilian woman from the northeastern state of Alagoas. The clinical history was typical of schistosomal infestation at the age of 8 years (papulous erythema in the skin of the legs after baths in a water contaminated with cercaria). From the age of 11 years until the present time the patient has had diarrheal episodes with pain in the left flank and softened stools containing mucus and blood. She had icterus at the age of 16 years, and this condition persisted for about one year. At that time the patient noted the appearance of splenomegaly (tumor at the left hypochondrium), increasing in size progressively. One year prior to admission, the patient noted soft edema in the legs, as well as some shortness of breath during exercise, and cyanosis of lips and fingernail beds which increased upon effort.

Physical examination revealed an underdeveloped patient, with infantile breasts and few hairs in the pubic region and none in the axillas; dyspnea, marked cyanosis, clubbing of the fingers, and slight edema of the legs. The lungs and the heart were normal, except for slight hyperphonesis at the pulmonary focus. The pulse rate was 92, and the arterial blood pressure was 110/70 mm. Hg. The liver and the spleen were enlarged and hard; the liver was palpable about 3 cm. below the right costal margin, and the spleen, 7 cm. below the left costal margin.

A number of laboratory and auxiliary tests were performed, and the most important findings are presented here. (1) There was a positive finding of schistosome ova in the stools. (2) The results of the pulmonary function tests are shown in Table I. The oximetric studies on the blood

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Received for publication June 11, 1959.
Presented in Associação Paulista de Medicina, Department of Medicine, April 30, 1958.

were repeated two times. The first study revealed an unsaturation of the arterial blood of 64 per cent, and the second, after the patient had been in the ward about 2 months, showed an unsaturation of 71 per cent. After the patient had received oxygen (98 per cent) for 10 to 12 minutes, arterial saturation rose to 89.4 and 96.7 per cent, respectively. (3) The electrocardiogram showed only sinus tachycardia (heart rate, 110 per minute). (4) The erythrocyte and leukocyte counts were 5,100,000 and 3,000 per cubic millimeter, respectively. Hemoglobin concentration was 14.7 Gm. per 100 ml. (92 per cent); color index 0.9; hematocrit reading 46 per cent; differential count of leukocytes showed: 56 per cent segmented forms, 6 per cent band forms, 18 per cent eosinophils, 13 per cent lymphocytes, and 7 per cent monocytes. (5) The serum chloride levels were 108, 109, and 129 mEq./L.; the CO_2 combining power was somewhat lowered (39.5, 33.8, 39 volumes per cent in plasma of venous blood). The serum proteins were normal. (6) In tests to determine liver function the cephalin-cholesterol flocculation test (Hanger) was 4 plus; thymol turbidity was 5 units (Maclagan); and thymol flocculation was 2 plus. Serum bilirubin per 100 ml. was: immediate direct, 0.6 mg.; total direct, 1.9; indirect, 1.7; and total bilirubin, 3.6. (7) X-ray studies of the lungs, heart, and great vessels showed the vascular markings in the lung fields forming a network, with wide meshes principally in the inferior parts. (8) The cardiac catheterization findings are given in Table II. There was a slight systolic pulmonary hypertension, with no change after exercise or inhalation of pure oxygen for 15 minutes. The diastolic pulmonary pressure was in the lower limits of normal and was reduced by physical exercise. The mean pressure in the right atrium and the diastolic pressure in the right ventricle were normal, not changing after exercise or inhalation of oxygen. The pulmonary "capillary" pressure was within the maximal limits of normal and there was no change after exercise. The pressure in the femoral artery was normal. There was marked unsaturation of the systemic arterial blood, without normalization after inhalation of pure oxygen. The slight oxygen consumption was due to the patient's small body surface. The cardiac output and the cardiac index,

TABLE I. PULMONARY FUNCTION TESTS*

Lung Volumes (predicted values):			
Inspiratory capacity	1,941 ml.	1,780 ml.	109.0%
Expiratory reserve volume	1,090 ml.	1,140 ml.	95.5%
Vital capacity	3,031 ml.	2,920 ml.	104.0%
Residual volume (RV)	735 ml.	730 ml.	100.0%
Functional residual capacity	1,825 ml.	1,870 ml.	97.5%
Total lung capacity (TLC)	3,766 ml.	3,650 ml.	103.0%
RV/TLC × 100	19.5%	19.6%	—
Dead space (anatomic; estimated)	135 ml.	—	—
Maximal Breathing Capacity:			
(MBC)	73.5 L./min.	76 L./min.	97.0%
Gaensler index	1.08	1.00	—
Ventilation:			
Tidal volume 468 ml.			
Frequency 15			
Minute volume 7.02 L./min.			
Alveolar ventilation 5.0 L./min. (4.1 L./min./M.^{2})			
Alveolar pCO_2 23.95 mm. Hg			
Alveolar pO_2 104.16 mm. Hg			
Pulmonary N_2 elimination rate (7 min.) 2.5% N_2			
About 2 months later: alveolar ventilation, 4.3 L./min./M.^{2}; alveolar pO_2, 105.9 mm. Hg; and pCO_2, 20.0 mm. Hg			

*The patient was 1.47 meters in height, weighed 36 kilograms, and had a body surface area of 1.22 square meters. The external temperature at the time of the tests was 19°C., and the barometric pressure was 698 mm. Hg.

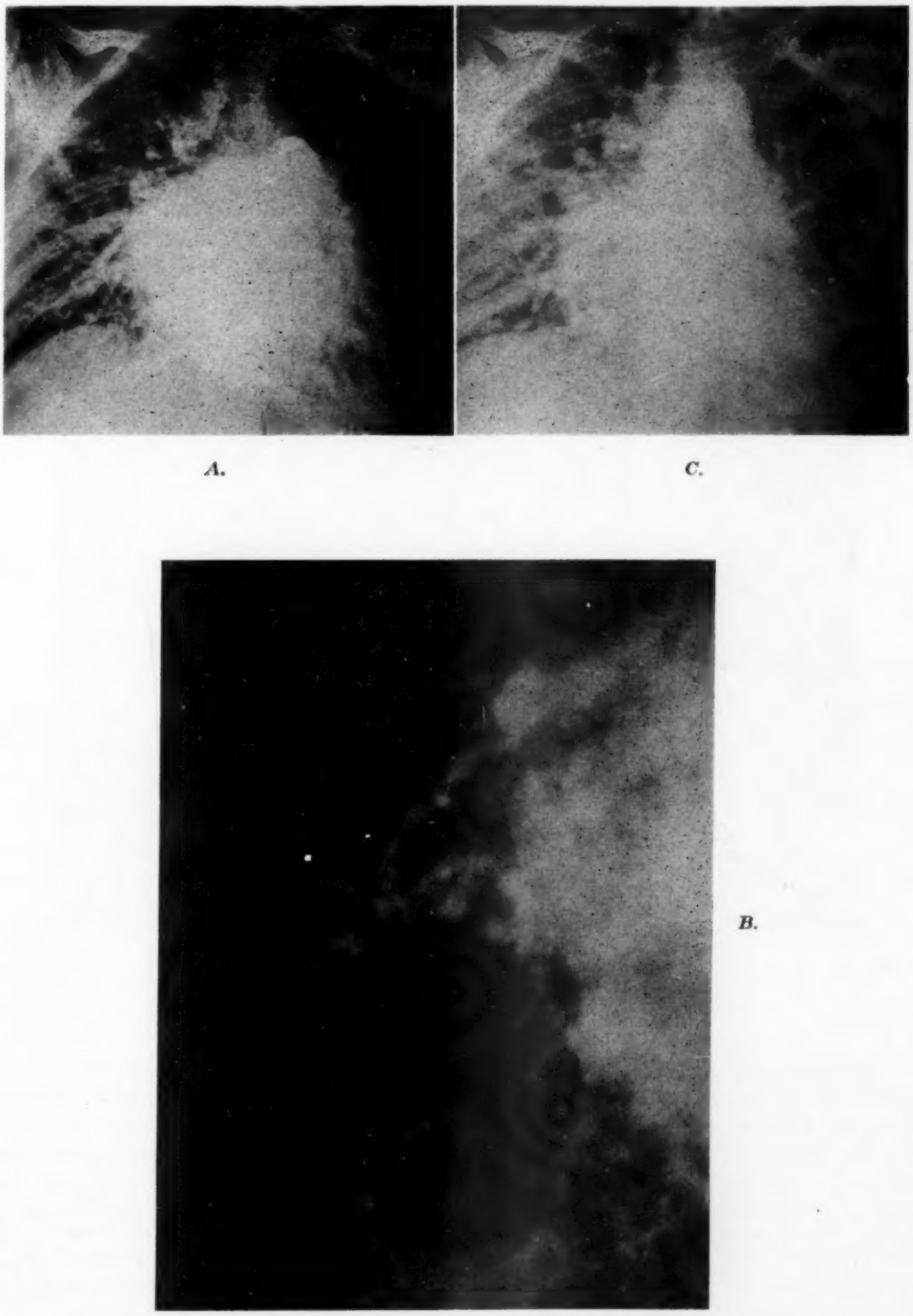
calculated by the Fick formula, were very high. Consequently, the total pulmonary resistance and the arteriolar pulmonary resistance were highly reduced. (9) Angiocardiography was performed by introducing the contrast medium (Opacoron 400, Casa Cilaq) into the left basilic vein (1 ml. per kilogram of weight) and taking the plates in the Angiocardiograph of Schönander at an interval of 1.3 seconds. The first plate (3.3 seconds) showed filling of the right heart chambers and the pulmonary artery and its main branches, revealing the vessels to be normal and the right atrium to be moderately increased in volume. In the second plate (4.6 seconds) the contrast medium was detected at the pulmonary artery truncus and chiefly at its branches. In addition, the lung fields presented a "lacework" aspect, resembling a granular pattern diffusely scattered, superposed on the arterial branches. The pulmonary veins and left atrium began to fill precociously (the latter in 2½ seconds; normal, 6 seconds) (Fig. 1). The third plate (5.9 seconds) showed good filling of the pulmonary veins, left atrium, left ventricle, and aorta. The latter was filled precociously (normal filling of the aorta, 8 to 9 seconds). The following plates showed only the elimination of the contrast medium.

Table II. Results of Intracardiac Catheterization

	Blood Pressures (mm. Hg)								
	At Rest			After Exercise			After O_2 Inhalation		
	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
Right atrium	—	—	3	—	-	5	—	-	4
Right ventricle	38	3	18	40	3	17	38	0	14
Pulmonary artery	35	8	18	39	4	16	—	-	—
Pulmonary "capillary"	—	—	13	—	-	11	—	-	—
Femoral artery	103	67	86	—	-	—	—	-	—

	Oximetry		
	O_2 Content (vol. %)	O_2 Saturation (%)	
Pulmonary artery	10.65	60.85	Oxygen consumption 141 ml./min.
Pulmonary artery after O_2	10.35	59.10	Cardiac output 25.6 L./min.
Femoral artery	11.20	64.00	Cardiac index 21.0 L./min./M.^{2}
Femoral artery after O_2	15.65	89.40	Total pulmonary resistance 50.5 dynes sec. cm.$^{-5}$
Maximal O_2 saturation	17.80	100.00	Arteriolar pulmonary resistance 11.2 dynes sec. cm.$^{-5}$
Hemoglobin (Gm./100 ml.)	13.50	—	

Lung Biopsy.—The sections revealed frequent schistosomal granulomas and small scars, the latter possibly resulting from the former, and both in the so-called parenchymatous localization (Fig. 2). The granulomas showed the classic histologic picture.[7,20] They were either recent or healing and healed. The scars were tiny, rounded, elongated, or irregular in shape, made up of collagenous tissue with round-cell infiltration and inconstant carbon particles. Frequently, the central or peripheral part of the scars showed very much dilated and conspicuous blood vessels with thin walls, resembling venous channels. Some scars were inconspicuous and appeared as a thickening around or near the small pulmonary arteries. In one of the random sections, which was more or less fusiform in shape, 6μ thick, about 1.3 cm. long, and 0.3 cm. in the broader part of the transversal axis, 9 schistosomal granulomas and 10 small parenchymatous scars were seen. In this section, one pulmonary arteriole (60μ in diameter) was observed to communicate in a small



A. *C.* *B.*

Fig. 1.—*A*, Angiocardiogram taken 4.6 seconds after the injection shows the plenitude of pulmonary vessels with a fine "lacework" aspect at the periphery. Pulmonary veins are filled and the left atrium begins to fill precociously. *B*, Detail of the "lacework" aspect seen in *A*, at the medial part of the right inferior lung field. *C*, Taken 5.9 seconds after the injection, showing the main venous trunks, the finer peripheral vessels, and a granular pattern. The left atrium is empty, the left ventricle is in systolic contraction, and the aorta has filled precociously. (Normally, filling of the aorta occurs 8 to 9 seconds after the injection.)

area with an adjacent venule (37μ in diameter) through an old destructive process in their walls (Figs. 3 and 4). The arterial structure was present in only a small segment of the wall, in which the elastica interna, the media, and the elastic externe were seen. Most of the wall failed to show the media and the elastic membranes, which were fused together. The arterial intima showed an intense and diffuse thickening, with conspicuous narrowing of the lumen, made up of young connective tissue with scattered lymphocytes. The adventitia was moderately thickened because of proliferation of fibrous tissue and lymphocytic infiltration. The fibrous tissue extended to the adjacent part of the venule wall. The latter was very thin, surrounded by the lung alveoli, and made up of the endothelial layer and adventitia, as well as a few subendothelial elastic fibers. These fibers were very thin, circular, and present only in a few points of the wall, where they formed an inconspicuous elastic membrane. The venule communicated with two adjacent pulmonary capillaries.

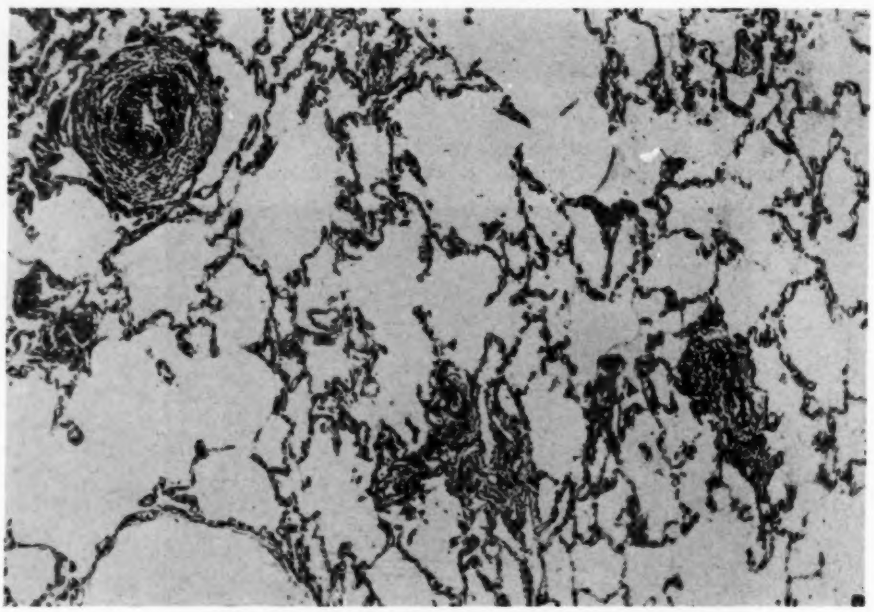


Fig. 2.—Lung showing a schistosomal granuloma (left upper corner) and two scars. Hematoxylin and eosin stain; ×64.

The serial sections, using the Weigert elastic tissue and van Gieson stains, showed that a few granulomas and the majority of the scars had been originated within, around, or beside the small pulmonary arteries and arterioles, which had been destroyed focally or diffusely throughout (Figs. 5 and 8). The diffusely destroyed arteries showed only remnants of their walls. These remnants, found in the granulomas and scars, were short segments of the whole wall, or, more frequently, only fragments of the elastic membranes. Healing granulomas showed in their periphery new vessels, which were seen occasionally to be in communication with the lumen of the destroyed artery (Fig. 8). These new vessels were made up only of swollen endothelial cells and basement membrane, and had either narrow or wide lumina. Vessels with wide lumina (about 19 μ in diameter) resembled venules and communicated with adjacent pulmonary capillaries.

A few of the wide vessels seen in the scars just described could be recognized in serial sections as originating in diffusely destroyed small pulmonay arteries (between 100 and 200 μ in diameter[11]). Such vessels had thin walls which where poorly delimited from the surrounding fibrous tissue. They were made up of endothelial lining and remnants of the elastic tissue of the primitive arterial wall. The elastic elements frequently either were present in only one part of the wall or failed to show up throughout the wall, appearing only in serial sections (Figs. 6 and 7). In other vessels

of the scars, however, remnants of the arterial wall were not found even after serial sections. In this case it was impossible to decide whether the wide vessel was originated in a branch of the pulmonary artery. Also found in the scars were wide capillaries of the venous type or venules in communication with the arterial lumen. The venules (about 30 to 37 μ in diameter) were made

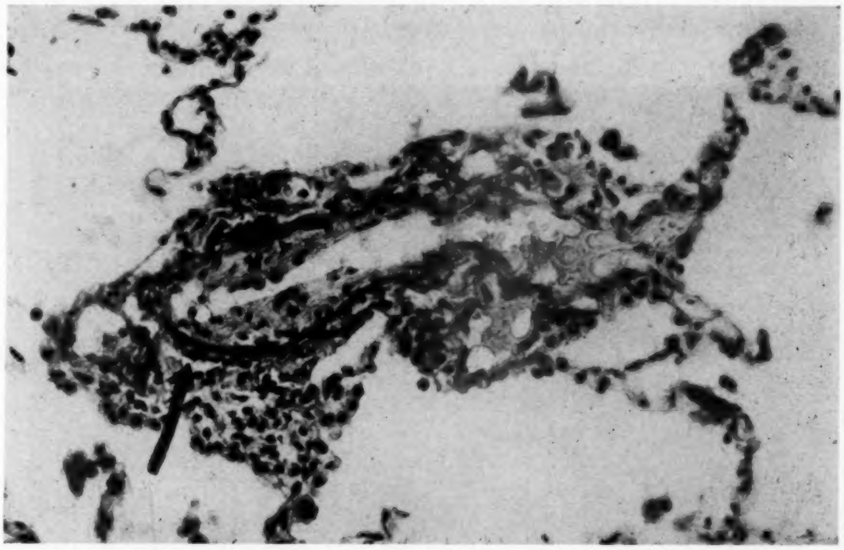


Fig. 3.—The scar seen at right in Fig. 2 (next section). Picture of arteriovenous fistula, presenting, at left, the arterial segment with thickened intima and adventitia. The arrow at the left points to the elastic membranes of the arterial wall. Weigert's elastic tissue and van Gieson's stains; ×413.

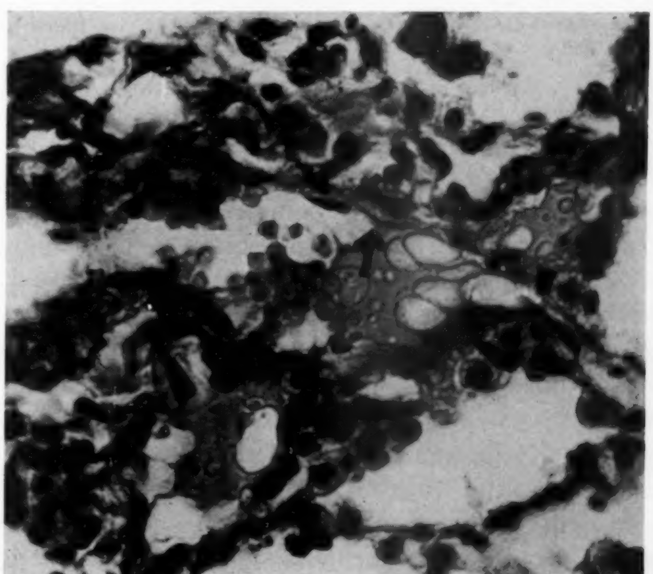


Fig. 4.—Detail of the venous segment seen in Fig. 3. The arrow points to the discontinuous elastic membrane; ×688.

up of endothelial cells, very thin and discontinuous circular elastic membrane, and scanty, inconstant, adventitial collagenous fibers (Fig. 8).

The small pulmonary arteries and arterioles related to the schistosomal granulomas and scars showed slight or moderate intimal fibrous thickening. This thickening was observed in a few of these vessels not related to those structures. An occasional picture of division of the arterial lumen by fibrous tract (recanalization) could also be seen. The wall of the pulmonary capillaries was thin. There was absence of pulmonary interstitial fibrosis.

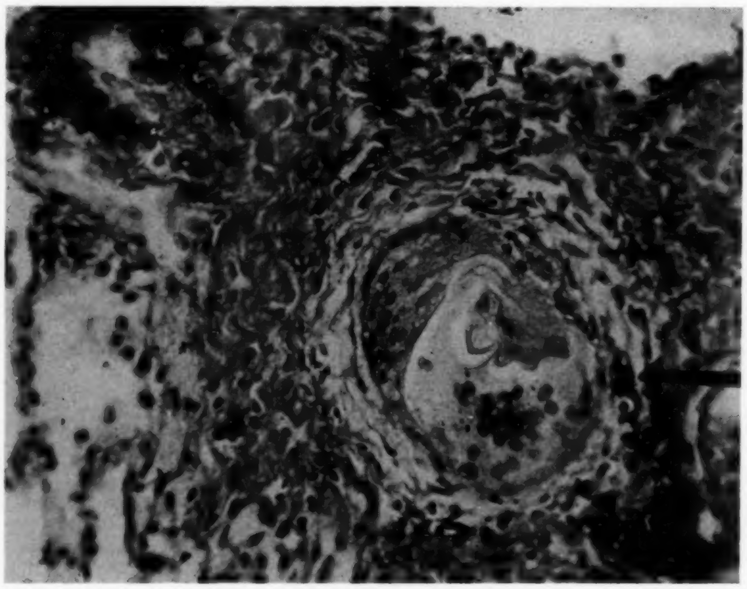


Fig. 5.—Schistosomal granuloma originated within a small pulmonary artery. Diffuse destruction of the arterial walls; only remnants of the elastic membranes are seen (arrow at the right margin). The elastic tissue of the destroyed artery (black spots can be seen at the left upper corner and the right lower corner). Weigert's elastic tissue and van Gieson's stains; ×384.

DISCUSSION

In this case of Manson's schistosomiasis the lung biopsy showed a marked process which was caused mainly by the schistosome ova. There were frequent granulomas and scars originating in the smaller branches of the pulmonary artery, and a fibrous endarteritis (Fig. 2). The latter was generally related to schistosome eggs, being nondiffuse in type, and did not produce conspicuous narrowing of the vascular lumina (Figs. 3 and 8). The slight pulmonary hypertension may be due mainly to obstruction in the arterial tree by schistosomal granuloma and endarteritis related to ova.[10-12]

The microscopic examination of the lung also revealed shunts between small pulmonary arteries and veins (Figs. 3 and 4). These shunts or arteriovenous fistulas may be caused, as previously described,[10,11] by the necrotizing action of embolic schistosome ova on pulmonary arteries and adjacent veins. In normal lungs,[6,17] arteriovenous communications characterized by thickened arteries are found. The thickening is due to an intimal cushion ("Intimapolster") constituted principally of longitudinal muscle fibers. The writers did not describe

direct anastomoses in the lungs, i.e., anastomoses without the intimal cushions,[6] except Hirsch,[18] whose work requires confirmation. In this case and others previously reported[11,13] the arteriovenous fistulas did not present either the peculiar picture of the normal arteriovenous anastomoses, nor glomic structures as described in pathologic cases.[27] Moreover, the arterial segment of the fistulas showed changes not found in the normal arteriovenous communications. These changes were an inflammatory fibrous thickening of the intima (fibrous endarteritis) and adventitia with a few inconstant round cells (Fig. 3).

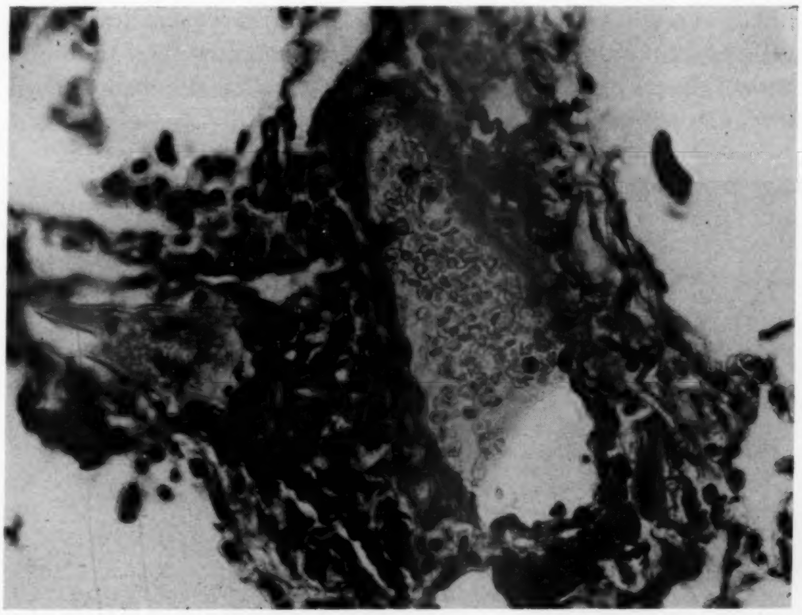


Fig. 6.—Vein-like vessel originated in place of diffusely destroyed artery, of which only remnants of the elastic membranes are seen (black spots in the vessel wall at right). Weigert's elastic tissue and van Gieson's stains; ×496.

In the lung biopsy of the present case we had difficulty in distinguishing precapillary from postcapillary, as has been the experience of other writers.[26,31] Such difficulty did not arise in cases of schistosomal cor pulmonale,[10,11] because the precapillaries frequently presented fibrous intimal thickening. In the present case the fistulas were between small arteries (between 100 and 200 μ in diameter[11]) and arterioles and venules (about 37 μ in diameter). The latter were vessels with very thin walls and a discontinuous elastic membrane made up mainly of circular fibers (Fig. 4). According to von Hayek,[17] the circular arrangement of the elastic fibers is a sure criterion for distinguishing these venous vessels from precapillaries, in which the elastic fibers are mainly longitudinal.

Besides these schistosomatic arteriovenous fistulas, there were smaller communications between small pulmonary arteries and vessels of the venous type. These smaller communications (about 19 μ in diameter) had thin walls and were comprised only of endothelial lining and basement membrane (Fig. 8). These vessels may be either venules without elastic membrane or giant venous capillaries.

The diameter of alveolar capillaries is 10 to 12 μ.[17] Schistosomatic arteriocapillary anastomoses have been described previously.[10,11]

In our earlier papers[10,11] we did not refer to a second possible mechanism of origin of the schistosomatic arteriovenous fistulas. Such a mechanism would be the organization of intra-arterial or para-arterial granulomas without necrosis of adjacent veins. Then, according to the observations in this case and those of Behmer,[4] in the organizing process of the schistosomal granulomas originating in the arterial lumen or para-arterially, after arterial necrosis, capillaries proliferate from the periphery. These new capillaries grow, communicate with the arterial lumen, and dilatate posteriorly (Fig. 8). At least a few of these capillaries may be of bronchial origin and, as is known, flow into pulmonary veins. In this connection we can cite the vascularization of the tuberculous caverns through bronchial vessels.[8]

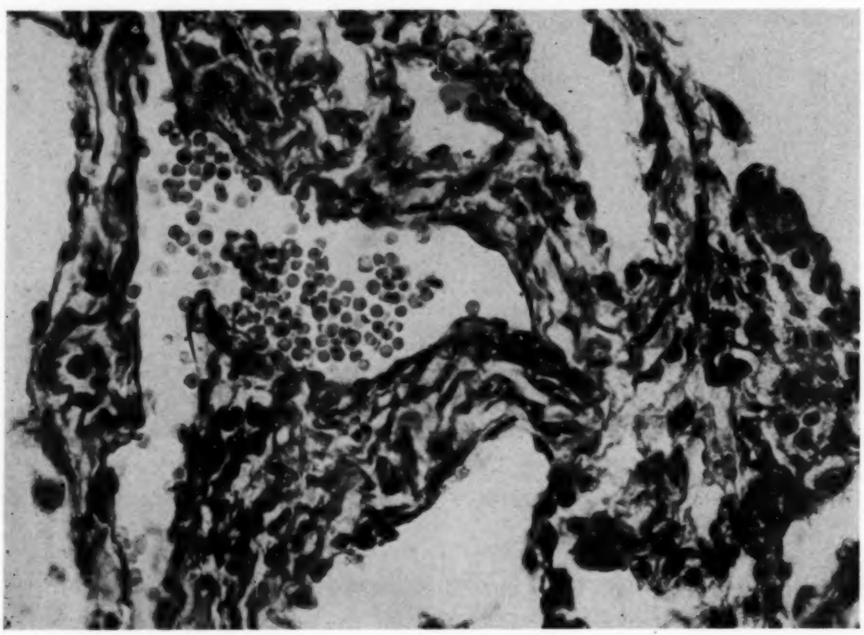


Fig. 7.—The scar seen at left in Fig. 2 (next section). Vein-like vessel communicating at left with a wide venous vessel. Weigert's elastic tissue and van Gieson's stains; ×544.

We wish to repeat that, even in the previously described[11] mechanism of origin of the arteriovenous fistulas after necrosis of the venous wall, these communications are not established at the beginning, directly, but through new capillaries formed in the granulation tissue appearing in the necrotic area (see Figs. 10 to 13 of our paper[11]).

Another frequent feature in the lung biopsy was the presence of parenchymatous scars with a central, very wide vessel in communication with adjacent veins and capillaries (Fig. 7). The vessel showed a venous structure, being the "angeiomatoid" of Shaw and Ghareeb.[29] In many instances we can say that it originated in the place of diffusely destroyed arteries, because the remnants of

the latter were found, as pointed out by Shaw and Ghareeb[29] (Fig. 6). In other instances the arterial remnants failed to show up even in serial sections. The histogenesis of such a vessel or "angeiomatoid" requires more research. According to the Egyptian authors[29] it originates from intimal occlusive tissue, and according to our observations, from healed intra-arterial granulomas or from thrombosed arteries.[11] In any case it is important to know that this "angeiomatoid" communicates with adjacent venous capillaries or veins as seen here (Fig. 7).

Of all these considerations it is apparent that the schistosomatic arteriovenous communications in this particular lung biopsy may be more frequent than we can say. The above-mentioned difficulties make their diagnosis uncertain. Also, investigations should be made to determine which of the two mechanisms referred to before is more important in the genesis of these fistulas.

Fig. 8.—Para-arterial healing granuloma with a venous vessel communicating with the arterial lumen. Weigert's elastic tissue and van Gieson stains; ×499.

Clinically, the patient presented a picture of late schistosomiasis, with hepatosplenomegaly, slight pulmonary hypertension, and marked cyanosis with clubbing of the fingers. The latter cannot be explained on the basis of a slight chronic cor pulmonale, because cyanosis is rare, even in well-established schistosomal cor pulmonale.[2,3,9,16,19,23,24,32] This case is similar to two others reported recently.[13] These three cases constitute the basis of a new cyanotic syndrome in pulmonary Manson's schistosomiasis, in which the main clinical sign is a marked cyanosis. The other signs are hepatosplenomegaly of late schistosomiasis, slight or absent pulmonary arterial hypertension, and a peculiar angiocardiographic picture. The histopathologic bases of the cyanosis are the schistosomatic pulmo-

nary arteriovenous fistulas. That these cases of schistosomiasis must be separated from the more common ones with marked pulmonary hypertension and slight or absent cyanosis was emphasized already by Lion and Andrade e Silva.[22]

Furthermore, the fistulas explain the results of the pulmonary function tests and cardiac catheterization, and possibly the angiocardiographic picture. The lung volumes were within normal values, as well as the RV/TLC $\times$ 100 relation and MBC. There was alveolar hyperventilation with low pCO_2 and high pO_2 within the alveoli, and unsaturation of the arterial blood that continued unsaturated after the patient had breathed 98 per cent oxygen for 10 minutes. These data show that there is no alteration in the broncho-alveolar system, but rather, a venous to arterial shunt in the heart or lung, with hyperventilation (the latter may be due to chemoreceptor reflexes initiated by anoxemia).

The arteriovenous fistulas explain the following findings obtained by cardiac catheterization, which showed, in addition, that the venous to arterial shunt was not in the heart: (1) no increase in systolic pulmonary pressure after exercise, because of the absence of a pulmonary arteriolar resistance; (2) decrease in the diastolic pulmonary pressure after exercise, because that resistance was failing; (3) absence of a decrease in pulmonary pressure after inhalation of pure oxygen, as normally occurs, because of arteriolar dilation; (4) unsaturation of arterial blood even after inhalation of pure oxygen (deviation of the blood through the fistulas without oxygenation in the pulmonary alveoli); (5) a great decrease in the arteriolar pulmonary resistance and total pulmonary resistance due to a great increase in the cardiac output and cardiac index (Fick's formula).

Angiocardiography revealed an unusual picture characterized by an aspect of diffusely scattered granulation in the lung fields (Fig. 1), as reported previously.[13] In addition there was a precocious filling of the pulmonary veins and left atrium. The retention of the contrast medium in the lungs for a longer time, as reported previously,[13] was not observed in this case. The cause of the granular aspect requires research in order to know whether it is due to larger arteriovenous fistulas.

So far we know that a similar angiocardiographic picture has not been described. The congenital arteriovenous aneurysms are gross structures and localized in certain areas of the lungs.[15,21,30] A congenital process involving the lungs diffusely is not referred to by the authors, except for a case reported by Sacrez and associates,[28] without microscopic study of the lungs. Giampalmo[15] suggests the possibility of the occurrence of a diffuse angiectatic state in the lungs, and the case reported by Apthorp and Bates,[1] with angiocardiographic study, would be of this nature.

Cases such as this are rare. More frequently in cases of pulmonary schistosomiasis the patients develop a pulmonary hypertension and the picture of chronic cor pulmonale.[11,23,24,25] However, the frequency of the well-developed cyanotic syndrome in schistosomiasis, as well as the slight forms of it, must be investigated. Cases of pulmonary hypertension and oxygen unsaturation of the arterial blood without apparent cause have already been reported.[5,14] We suggest that in patients with schistosomiasis presenting cyanosis without evident cause the possibility of schistosomatic arteriovenous fistulas must be investigated.

SUMMARY

A case of pulmonary Manson's schistosomiasis with marked cyanosis, clubbing of fingers, and slight pulmonary hypertension is reported. The lung biopsy showed frequent changes caused by schistosome ova and schistosomatic arteriovenous fistulas. These fistulas are the major factor in the genesis of the cyanosis and explain the results of the pulmonary function tests and cardiac catheterization, and possibly the peculiar angiocardiographic picture. On the basis of this case and two previously reported ones the present authors have postulated a new cyanotic syndrome in pulmonary Manson's schistosomiasis, characterized by hepatosplenomegaly, marked cyanosis, slight or absent pulmonary hypertension, and a peculiar angiocardiographic picture.

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Acute Idiopathic Pericarditis

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INTRODUCTION

In 1942, Barnes and Burchell[1] reported fourteen cases of what they considered to be a distinct syndrome, acute idiopathic pericarditis. They demonstrated the clinical similarity of idiopathic pericarditis to acute myocardial infarction and the value of the electrocardiogram in the differential diagnosis. This problem of differential diagnosis is re-emphasized by the present report, which analyzes fifteen cases of idiopathic pericarditis, with a report of one typical case. The patients were admitted to the hospital between 1951 and 1958, with an admitting diagnosis, in most cases, of acute myocardial infarction. Emphasis is given the clinical findings which aid in such a diagnosis. Furthermore, the presence of S-T segment depression in Lead aV_R of the electrocardiogram is stressed because of its importance in proper diagnosis, and therefore prognosis, and treatment.

CASE REPORT

The following case is illustrative of the diagnostic problem.

First Admission.—The patient, a 53-year-old white male truck driver, was admitted to Beth Israel Hospital on June 19, 1957, complaining of severe pain in the left lower chest, aggravated by deep inspiration, and beginning 14 hours prior to admission. The patient had a few similar attacks beginning some 25 years before, and for one of these attacks he had been hospitalized elsewhere and told that he had "pleurisy." Interval chest x-rays taken between attacks revealed diffuse clouding over the left lower lobe, which was described as a pleural reaction. The electrocardiogram was within normal limits. On admission, physical examination revealed decreased breath sounds and dullness to percussion over both posterior pulmonary bases, with decreased tactile and vocal fremitus in the same areas. No friction rub was noted. His temperature was 101°F., and chest x-ray revealed bilateral pleural effusions.

The patient was treated with penicillin, and the pleural effusions cleared by June 24, 1957. At that time the heart was noted to be enlarged in its transverse diameter. He was discharged, asymptomatic, on June 27, 1957, with no electrocardiographic abnormalities noted. The final diagnosis was bronchopneumonia with pleurisy and bilateral pleural effusions.

Second Admission.—The patient was readmitted on Nov. 15, 1958, because of the sudden onset of squeezing retrosternal pain which radiated to the left arm. He had been treated with tetracycline for a left "pleuritis" several days prior to admission. The pulse rate was 110; the temperature was 102°F.; the blood pressure was 130/90 mm. Hg; and the respiratory rate was 22. He

Received for publication May 25, 1959.

appeared acutely ill. Minimal râles were heard at the left posterior pulmonary base. Heart sounds were of diminished intensity and no rub was audible. Chest x-ray revealed obliteration of both costophrenic sinuses. The electrocardiogram revealed elevation of the S-T segment in Leads I and II, aV_L, and V_4 through V_6, and was interpreted as suggestive of anterior wall myocardial infarction. Complete blood count was within normal limits. Serial electrocardiograms revealed an elevation of the S-T segment in Leads I, II, aV_L, aV_F, and V_3 through V_6 and depression of the S-T segment in Lead aV_R (Fig. 1); and subsequent inversion of the T wave in Leads I, II, aV_L, aV_F, and V_2 through V_6, with an upright T wave appearing in Lead aV_R (Fig. 2). Serial sedimentation rates varied from 30 to 98 mm. per hour (Westergren), and serial serum transaminase determinations varied from 23 to 66 units.

The patient was treated for acute anterior wall myocardial infarction and was started on Dicumarol. The drug was stopped after 10 days because of the appearance of hematuria. Digitalis and diuretics were added because of persistent basilar râles, which were interpreted as evidence of congestive heart failure.

The patient slowly improved. The chest x-ray was normal on December 17, and he was discharged, asymptomatic, on Dec. 20, 1958. A follow-up electrocardiogram taken 10 weeks after the onset of illness was similar to his pre-illness tracing.

COMMENT

This case is presented to emphasize the diagnostic problem which still exists between acute myocardial infarction and acute idiopathic pericarditis. Severe chest pain was the outstanding symptom, and because the electrocardiogram was abnormal, acute myocardial infarction was considered. The patient was started on Dicumarol. However, serial electrocardiograms revealed further elevation of the S-T segments, and a pattern compatible with acute pericarditis evolved, which was then considered to be the cause of the changes seen on the tracings.

Two of the twelve-lead electrocardiograms taken in this case are reproduced here. Fig. 1, taken 2 days after admission, reveals the elevated S-T segments (concave upward) and the depression of the S-T segment in Lead aV_R. Fig. 2, taken 21 days after admission, reveals the inverted T waves and an upright T wave in Lead aV_R.

MATERIAL

Following is a summary of the findings in the fifteen cases of acute idiopathic pericarditis reviewed. The fifteen patients were admitted to the hospital between 1951 and 1958: in 1951, two; in 1952, three; in 1953, two; in 1954 and 1955, none; in 1956, one; in 1957, one; and in 1958, six. The age range was 19 to 64 years, with an average of 43.2 years. There were thirteen men and two women (Fig. 3). Conventional twelve-lead electrocardiograms were taken on all patients and chest x-rays were taken on all except one patient during their stay in the hospital. Follow-up electrocardiograms after discharge were taken on all but three of the patients.

RESULTS

Clinical History.—All of the patients had pain, a pericardial friction rub, and/or a characteristic electrocardiographic pattern,[5,22] and no specific demonstrable cause of pericarditis was seen, as was true in the study of Reid and associates.[4] In those patients in whom it could be determined, six had antecedent upper respiratory infections, one had diarrhea and fever, and one had nonspecific aching and malaise. All complained of chest pain, but nine described it as dull

and pressing, six as sharp, and two as pulsating. Some patients had more than a single component to their pain pattern. The pain was located substernally in eleven of the patients. Other inclusive sites were the shoulder or shoulders in seven, the neck in four, the arm or arms in three, the epigastrium in three, and the precordium in two patients. The chest pain was made worse by deep breathing in eight patients and by change of body position in six.

Clinical Findings.—Forty per cent of the patients had a maximum pulse rate below 100, and sixty per cent had a rate above 100 per minute. A friction rub was heard at some time during the illness in eight patients and not heard at all in seven. The maximum temperature in each case was 99 to 104.9°F. Four patients had a temperature between 99 and 100.9°F., and in eleven it was between 101 and 104.9°F. Eighty-seven per cent of the patients had a temperature above 99.9°F.

Laboratory Findings.—The white blood count was below 10,000 per c.mm. in twenty per cent and above that figure in eighty per cent of the patients. Seven patients had a leukocytosis in the range of 14,000 to 19,000 per c.mm. The maximum sedimentation rate (Westergren: normal below 20 mm. per hour) was below 20 mm. in four and above 20 mm. in eleven cases. It was within the range of 60 to 120 mm. in nine cases. The maximum transaminase (when determined) was below 40 units in four patients and above 40 units in four. The highest reported result was 66 units. The chest x-ray revealed an enlarged heart in fifty per cent of the patients (taken in fourteen patients). Pulmonic infiltrations were present in three patients (one unilateral and two bilateral). Pleural effusions were noted in five patients (one on the left, two on the right, and two bilateral).

Electrocardiographic Findings.—S-T segment alterations characteristic of pericarditis were present in the electrocardiograms of thirteen of the fifteen patients.[5-7,8,22]

S-T segments: Of the fourteen patients who showed electrocardiographic changes, thirteen showed S-T segment elevations. (One showed only T-wave inversions, but the first electrocardiogram was taken 3 weeks after the beginning of illness and, hence, probably missed the S-T changes.) All showed at least a 1-mm. S-T segment depression in Lead aV_R at some time during the course of their hospital stay, and most within 3 days of the beginning of their illness (Fig. 1) (except one patient in whom only a single electrocardiogram was recorded). Lead I or Lead II, or both, usually showed the S-T segment elevations for the longest period of time. Elevations in the S-T segment were noted in Lead aV_L in six cases, in Lead aV_F in five cases, and in both of those leads in a single case. The duration of the S-T segment elevation from the beginning of the clinical illness was from 2 to 13 days (in those cases in which it could be determined from the information available).

T wave: In general, the T-wave inversions followed the S-T changes, with either no overlap or a mild degree of overlap. (In two cases the S-T changes reverted to completely normal before precordial T-wave inversions were noted.) T-wave changes did not occur or were probably missed because of the patient's discharge from the hospital in a few cases. In one case, at least 28 days of illness

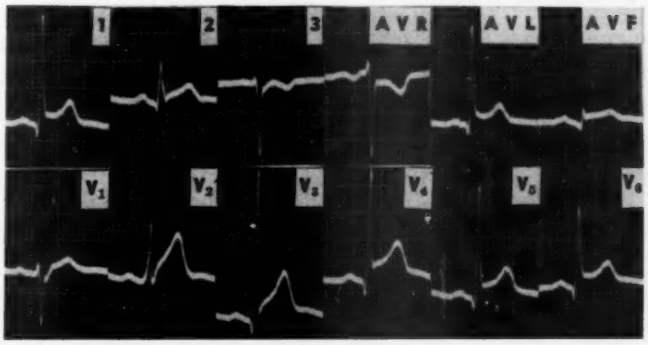

Fig. 1.—Electrocardiogram taken on Nov. 17, 1958, two days after admission. Note the S-T segment depression in Lead aVR.

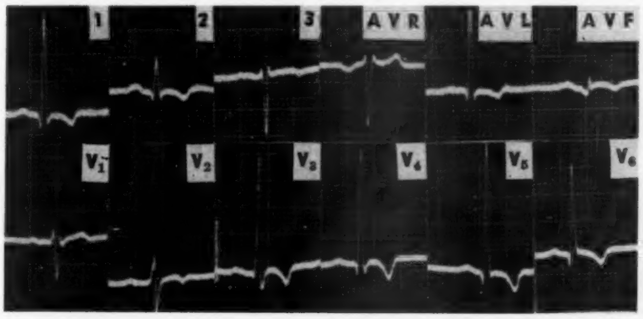

Fig. 2.—Electrocardiogram taken on Dec. 6, 1958, nineteen days after admission. Note the upright T wave in Lead aVR.

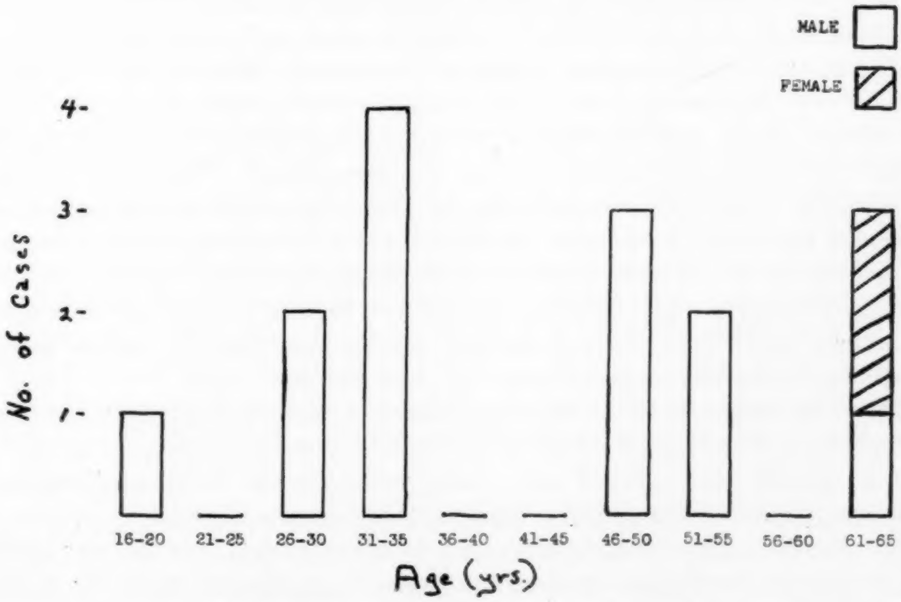

Fig. 3.—Age and sex distribution of the fifteen patients.

elapsed before precordial diphasic T waves appeared. When T-wave changes were seen in the precordial leads (peaking of T waves progressing to actual inversions), Leads V_2 through V_6 were usually involved on any single tracing (Fig. 2). The known length of time during which characteristic T-wave changes persisted in precordial leads (tall, peaked T wave followed by T-wave inversion) was, at the most, 65 days. The time elapsing before the precordial T-wave inversions appeared after S-T segment elevations were first noted (when such could be determined) was, at the most, 54 days.

A pericardial friction rub, when present, was heard before or during the S-T segment changes and disappeared by the time the precordial T-wave inversions were noted. Eleven patients subsequently reverted to a normal or to their pre-illness tracing (three patients could not be contacted for a follow-up electrocardiogram).

DISCUSSION

Since the etiology of this disease process, thought to be based on a virus or on hypersensitivity,[9,19] is as yet unproved, and its manifestations as an acute problem are being seen and diagnosed more often, the further report of groups of these cases serves to keep the physician aware of it. Moreover, the major differential possibility is acute myocardial infarction, and anticoagulants are usually contraindicated if acute pericarditis is present.[3]

Although thought to be a disease of young adults, it is found to be reported more and more in increasing ages up to the coronary age group. The mean age for cases in this report was 43.2 years; thirteen of the fifteen patients were men.

Over fifty per cent of the patients reported some prodromata, and forty per cent reported a pre-existing upper respiratory infection. Whether the medicinal therapy of these prodromata contributes to the incidence of this disease process, in light of the antibiotic era, could not be determined in this study.

The location of the pain usually revealed a substernal component, but twenty per cent of the patients had an epigastric component. Instances have been reported of confusing acute abdominal clinical pictures in cases of acute idiopathic pericarditis. Some patients have even undergone laparotomy, which indicates the confusion generated by the process at these times.[10] The character of the pain is difficult to differentiate from that due to coronary occlusion, but sixty per cent of the patients reported exacerbation of pain on deep inspiration and/or on changing bodily position, which is an important differential point.

A pericardial friction rub may or may not be heard, is usually evanescent, and lasts for a short time during the acute phase. Levy and Patterson[9] reported persistence of the friction rub from 1 day to 4 weeks.

Fever is usually seen as part of the clinical picture (eighty-six per cent in this report), and tachycardia may or may not be present. The total white blood count is usually above 10,000 per c.mm., although the differential follows no consistent pattern and is usually relatively within normal limits.

The erythrocyte sedimentation rate is usually elevated, and the transaminase may be normal, borderline, or elevated, probably dependent upon the degree of subepicardial myocarditis present.[11,12]

The chest x-ray may or may not reveal an enlarged heart (probably due to pericardial effusion in most cases), which later usually reverts to normal size. One patient in this report had a definite pericardial effusion which was proved by angiocardiography and later aspirated (500 c.c. of straw-colored fluid). Pulmonary infiltrations and pleural effusions may or may not accompany the disease process.

Electrocardiographic changes of pericarditis have been described by many authors, and are usually noted if serial electrocardiograms are taken. The typical changes include early elevation of the S-T segments, with more or less upward concavity, in Leads I, II, aV_L, and/or aV_F and usually in the precordial leads, with S-T segment depression in Lead aV_R (Fig. 1). This is understandable, since in acute pericarditis the ischemic effect involves the epicardial layers of the ventricles, and the abnormal S-T vector points toward the center of the involved area (approximately 60°). Hence, the S-T vector has a direction away from the right arm lead.[23] The T waves are usually tall and peaked (or dome-shaped) in the precordial leads early in the course of illness, and then go on to final peaked inversion. Hence, the T-wave vector at the time of generalized T-wave inversion will point in the direction of the right arm (approximately 320°) and away from the affected region of the heart, the T wave becoming positive in Lead aV_R (Fig. 2). Negative T waves in the bipolar and limb leads in which S-T segment elevations were previously noted are usually seen if serial electrocardiograms are taken (Fig. 2), but may be missed or may not necessarily occur.

I should like to emphasize that all patients included in this report in whom electrocardiographic changes were noted, showed at least a 1-mm. S-T segment depression in Lead aV_R (Fig. 1), usually early in the course of their illness during the phase of S-T elevation in the bipolar leads and before actual T-wave inversion in the precordial leads. This point is stressed because of its value in the differential diagnosis when no Q waves are seen. Patients who suffer myocardial infarctions might show, but less frequently, early depression of the S-T segment in Lead aV_R, and when myocardial infarction is present, will many times show concomitant S-T segment depression in Lead aV_L and Q waves will be noted. However, it is also possible that in pericarditis occurring with myocardial infarction the S-T segment in Lead aV_R may be depressed. Differences in the RS-T segment are also noted as mentioned by Lepeschkin: "When an elevation of RS-T is present in pericarditis, an S wave previously present is not obliterated, but pulled up, so that it forms a notch between the R wave and the elevated RS-T segment. In myocardial infarction, the elevation of RS-T always obliterates the S wave and begins directly from the descending limb of the R wave."[5] This notching is noted in Fig. 1 in Leads II, V_3, and V_4 in the case reported here.

It is important to note that S-T segment changes may be quite evanescent, and in the cases reported they lasted anywhere from 2 to 13 days from the beginning of the clinical illness. However, Krook[13] noted S-T segment changes which persisted for 3 to 5 weeks in three cases; Scherl[2] reported a case in which

they persisted for 6 weeks; Feder,[14] a case in which S-T segment changes persisted for 3 months, and Coffen,[15] a case in which persistence was noted for 6 months.

In this series of cases it was noted that it may be as much as 5 weeks before precordial T-wave inversions are seen after the S-T segment elevations become manifest. The precordial T-wave changes, including peaking, degrees of inversion, and return to normal, may persist for as long as 7 weeks. Godfrey,[16] however, reported three cases with evidence of persistent myocardial damage after acute nonspecific pericarditis, and in one of these cases the T-wave change still persisted for 2½ years after the original illness. All patients in the present report in which follow-up was possible (eleven cases) had eventual electrocardiographic reversions to the normal or pre-illness tracing. No arrhythmias complicated the course of these patients, but arrhythmias have been observed by others in previous reports, and included auricular fibrillation, paroxysmal auricular flutter, supraventricular tachycardia,[13] and ventricular tachycardia.[20] Gallop rhythm has also been noted.[18] In general, the prognosis is good. However, Krook[13] reported two cases in which chronic constrictive pericarditis followed the onset of illness by 6 and 20 months, respectively; these patients were subsequently benefited by surgery, and microscopic examination of the operative specimens showed no signs of specific inflammation.

Recurrences are not uncommon, and are reported occurring as late as 8 to 10 years after the first attack.[9]

Treatment in these cases consisted of the use of various antibiotic preparations—a diuretic and digitalis in one case—but was otherwise of nonspecific supportive type. However, in one case, a recurrence was noted approximately 1½ months after the first attack, and the patient was treated with prednisone, with good results. Some patients have done well with aspirin therapy and/or aminopyrine preparations.[18] ACTH and cortisone have been reported to produce dramatic improvement in some cases,[21] an improvement which is probably due to a nonspecific anti-inflammatory effect which helps the patient through the acute phase of the disease process.[19] Also, the rebound phenomenon has been noted after therapy is reduced or stopped abruptly and/or prematurely, as is noted in the steroid therapy of acute rheumatic fever.

It is of interest to note how closely cases of postmyocardial-infarction syndrome and postcommissurotomy syndrome resemble the manifestations of idiopathic pericarditis (especially the former), as has been reported by Dressler.[17] Whether these manifestations have some etiologic factors in common remains to be shown. Anticoagulant usage appears to be contraindicated in the management, and steroids may prove to be of value in more cases if more widely tried.[21]

SUMMARY

The manifestations of acute idiopathic pericarditis in fifteen patients have been presented, and a typical case has been reported. The pertinent current literature has been reviewed briefly.

The various electrocardiographic findings in acute pericarditis are discussed, and reference is made to the vector explanation of these changes.

Since acute myocardial infarction is paramount in the differential diagnosis of this entity, emphasis is placed on finding depression of the S-T segment in Lead aV_R of the electrocardiogram when Q waves are absent and when the other described changes are present.

I am indebted to Dr. Seymour Rinzler and Dr. Harry Vesell for their helpful criticism and advice, to Dr. Jay Miller for permission to illustrate his case, and to those physicians whose cases I reviewed.

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Experimental and Laboratory Reports

The Relationship Between Pulmonary Arterial Pressure and Roentgenographic Appearance in Mitral Stenosis

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Enlargement of the pulmonary arterial segment of the cardiac silhouette is a common roentgenographic finding in mitral stenosis. Since the segment is essentially a passive, distensible conduit for blood, the pressure within it should be one of the main determinants of its size.

It has been shown in the past[1-3] that the pulmonary artery enlarges with pulmonary hypertension and excessive pulmonary blood flow. Healey and associates[1] concluded from studies in patients with and without left-to-right shunts that increased flow in itself at or near normal pressure does not lead to appreciable enlargement of the pulmonary arterial segment unless the cardiac index exceeds 7 liters per minute per square meter of body surface area. Thus, flow as a distending factor does not play an important part in cases of mitral stenosis, in which the cardiac index is rarely if ever of such magnitude.

Precise correlations between pulmonary arterial pressure and size were not established in these studies, in which arbitrary grading scales rather than reproducible objective measurements were used to describe the size of the pulmonary artery. Nevertheless, Davies and co-workers[3] concluded, from angio-

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This work was supported by grants from the Life Insurance Medical Research Fund and the National Heart Institute, U. S. Public Health Service (Grant No. H-450).

Received for publication June 15, 1959.

*Work done during the tenure of a Fellowship from the Massachusetts Heart Association.

**Work done during the tenure of a Postdoctoral Fellowship from the Life Insurance Medical Research Fund.

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****Work done during the tenure of a Postdoctoral Fellowship from the National Heart Institute, National Institutes of Health.

cardiographic studies, that the x-ray appearance of the pulmonary artery was a better guide to the diagnosis of pulmonary hypertension than were clinical or electrocardiographic findings. Quantitative measurements on the roentgenogram were made by Schwedel and associates,[4] who examined the diameter of the right descending pulmonary arterial branch in 105 patients with mitral stenosis and found a rough correlation with pulmonary arterial mean pressure when the branch was enlarged, but pulmonary hypertension was also present in many subjects in whom the size of this vessel was within normal limits. Soloff and co-workers[5] determined the diameter of the pulmonary artery in 25 patients with mitral stenosis by biplane stereovenous angiography and noted that it correlated better with pulmonary arterial mean pressure (r = 0.765) than with any other hemodynamic parameter.

An attempt was made in the present study to find an easy, reproducible method for appraising pulmonary arterial size on the plain roentgenogram which might provide a good correlation with pressure. Ozawa[6] has described a simple measurement on the posteroanterior film of the chest which defines quantitatively the prominence of the pulmonary arterial segment. The present communication is concerned with the application of this measurement in a series of patients with mitral stenosis, and examines its usefulness with regard to the recognition of pulmonary hypertension from the radiologic appearance.

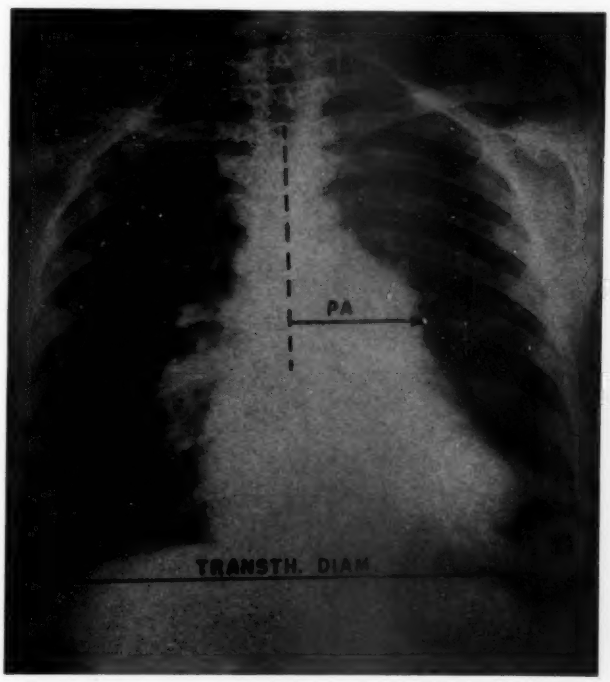

Fig. 1.—Determination of the pulmonary artery/chest ratio. ***PA*****: Size of the pulmonary arterial segment, in centimeters, measured from the midline, as defined by the thoracic spines, to its most prominent point on the left cardiac border.** ***Transth. Diam.:*** **Greatest transthoracic diameter, in centimeters, measured from pleura to pleura.** $\text{PA/Chest Ratio} = \frac{\text{PA}}{\frac{1}{2}\ \text{Transth. Diam.}} \times 100.$

TABLE I

PATIENT NUMBER	PULMONARY ARTERIAL SIZE (CM.)	PA/CHEST RATIO (%)	PULMONARY ARTERIAL MEAN PRESSURE (MM. Hg)
1.	2.8	20	16
2.	2.9	18	19
3.	2.8	19	20
4.	3.5	29	22
5.	3.0	20	25
6.	3.8	14	26
7.	3.9	29	29
8.	3.8	29	30
9.	4.5	36	32
10.	4.8	32	33
11.	5.2	34	33
12.	4.0	30	35
13.	3.5	29	36
14.	6.2	45	38
15.	5.8	40	43
16.	6.2	45	43
17.	4.0	29	44
18.	3.8	31	45
19.	4.5	36	46
20.	4.3	31	47
21.	4.8	38	48
22.	4.9	40	48
23.	7.2	49	48
24.	5.9	49	50
25.	6.6	53	50
26.	5.0	41	54
27.	4.8	39	55
28.	6.4	44	55
29.	5.2	40	57
30.	5.0	42	57
31.	5.9	46	58
32.	5.8	49	58
33.	6.0	42	59
34.	6.9	47	60
35.	7.6	51	60
36.	6.0	46	61
37.	5.8	49	61
38.	6.1	48	62
39.	5.5	47	64
40.	5.5	47	65
41.	6.0	43	67
42.	6.2	46	67
43.	7.0	48	69
44.	6.8	53	71
45.	7.0	53	71
46.	7.0	53	71
47.	8.0	56	71
48.	7.1	58	72
49.	6.5	48	74
50.	6.5	47	75
51.	8.0	65	77
52.	6.2	53	80
53.	6.4	49	81
54.	9.0	59	81
55.	7.2	53	90
56.	7.4	58	91

MATERIAL AND METHODS

Fifty-six adult patients with mitral stenosis, as determined by clinical and cardiac catheterization findings, were studied. The diagnosis in all was subsequently confirmed at surgery. The group contained no individuals with complicating conditions which might alter the x-ray appearance of the pulmonary arterial segment. Specifically, patients with spinal or thoracic deformities, left ventricular enlargement, aortic valvular disease, significant mitral regurgitation, or previous thoracic surgery were excluded. Pulmonary arterial pressures were measured through a cardiac catheter, utilizing a Statham P23D strain gauge manometer and a Sanborn Poly-Viso recorder. Mean pressures were obtained by electrical integration. The zero point for pressure measurements was 10 cm. anterior to the back, at the level of the seventh thoracic vertebra in the supine position.

A standard 7-foot posteroanterior film of the chest of each patient, taken within 3 to 4 days of the time of cardiac catheterization, was examined and the following measurements were made: (1) transthoracic diameter, i.e., the greatest transverse diameter of the chest from pleura to pleura, in centimeters; (2) "pulmonary arterial size," i.e., the distance from the midline, as judged by the thoracic spines, to the edge of the pulmonary arterial segment at its widest point, in centimeters (Fig. 1). From these measurements the "PA/chest ratio" was calculated as follows[6]:

$$\frac{\text{"Pulmonary Arterial Size"}}{\frac{1}{2}\ \text{Transthoracic Diameter}} \times 100$$

This calculation corrects for variations in body size by expressing the prominence of the pulmonary arterial segment as a percentage of the diameter of the hemithorax.

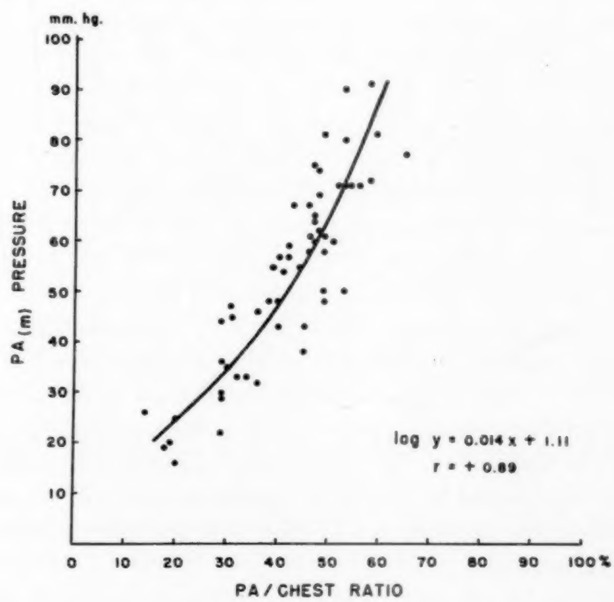

Fig. 2.—Relationship between pulmonary arterial mean pressure and PA/chest ratio as determined from the chest film. The regression equation is an exponential function. The regression line resembles a pressure-volume curve.

RESULTS

The data for pulmonary arterial size, PA/chest ratio, and pulmonary arterial mean pressure are listed in Table I.. Pulmonary arterial mean pressure is plotted against the PA/chest ratio in Fig. 2. A positive correlation is evident (r = +0.89).

The regression is exponential and resembles a pressure-volume curve. When uncorrected pulmonary arterial size is plotted against pressure, the scatter is considerably greater and the relationship less clear.

The measurements from the roentgenogram were also plotted against pulmonary arterial systolic pressure, pulmonary arterial diastolic pressure, pulmonary "capillary"[4] pressure, pulmonary vascular resistance, and cardiac index. The correlations obtained from these plots were much poorer than those with pulmonary arterial mean pressure.

DISCUSSION

Whereas the measurement of pressure in the pulmonary artery can be made with a high degree of accuracy, it is necessary to examine the factors which are likely to influence the measurement of pulmonary arterial size as employed in this study. Obviously, the measurement is not the true diameter of the pulmonary artery. The term "pulmonary arterial segment" refers to the convexity of the upper left border of the cardiac silhouette above the left atrium and below the aortic knob. The waist of the heart here includes the aorta, main pulmonary artery, and part of the left pulmonary artery. In taking the measurement from the midline, as defined by the thoracic spines, to the left-most point of the pulmonary arterial segment, possible variations due to widening of the aortic shadow are minimized. On the other hand, the left atrial and right ventricular enlargement commonly seen in mitral stenosis may tend to alter the anatomic relationships of the pulmonary artery and "push up" on the pulmonary arterial segment so that it may appear larger without actually being increased in size. Further potential distorting factors which may influence the appearance of the pulmonary arterial segment would be rotation of the heart due to various chamber enlargements, alteration of the silhouette by elevation of the diaphragm secondary to ascites and hepatomegaly, pleural or pericardial effusion, and perhaps lymphedema of the wall of the pulmonary artery itself. Despite these objections concerning the proper anatomic definition of the measurement on the chest film, the method provides a correlation between pulmonary arterial pressure and size which is superior to that obtained with more arbitrary grading systems or measurements which do not correct for variations in chest size. Moreover, the resemblance of the regression line to a pressure-volume curve suggests that the relationship is basically determined by the distensibility characteristics of the pulmonary arterial segment.

This method cannot be extended indiscriminately to other diagnostic groups in which enlargement of the pulmonary arterial segment may be associated with pulmonary hypertension. Healey and associates[1] have pointed out that the effects of increased pressure and increased flow or any combination of the two on the size of the pulmonary arterial segment cannot be differentiated. In cases of left-to-right shunts and high pulmonary blood flow, for example, a prominent pulmonary arterial segment may be found with only moderate increase in pulmonary arterial pressure, whereas the same degree of prominence of the pulmonary artery in cases of Eisenmenger's syndrome may be associated with low

pulmonary blood flow and pulmonary arterial pressures equal to systemic blood pressure. The appearance of the distal pulmonary vasculature must be considered together with the prominence of the pulmonary arterial segment in these cases, and even then the level of pulmonary arterial pressure is difficult to predict from the roentgenogram. In cases of the cyanotic forms of chronic cor pulmonale secondary to pulmonary parenchymal disease the cardiac index may likewise be significantly increased. Also the associated pulmonary emphysema in these cases tends to alter the configuration of the thoracic cage and cardiac silhouette, leading to unpredictable changes in the PA/chest ratio.

On the other hand, in a homogeneous diagnostic group such as that of cases of mitral stenosis, in which the cardiac index is quite uniformly reduced or at low normal levels and pulmonary emphysema is not a factor, the PA/chest ratio allows a fairly accurate estimate of the pulmonary arterial pressure. In our hands, it has been a more useful index to the presence or absence of pulmonary vascular disease than have the clinical or electrocardiographic data. Thus, this simple measurement can be considered a helpful tool in the preoperative evaluation of patients with mitral disease, and may further reduce the need for cardiac catheterization.

SUMMARY

1. The prominence of the pulmonary arterial segment on the postero-anterior chest x-ray in a group of 56 patients with mitral stenosis was assessed by calculation of the "PA/chest ratio." The distance from the midline, as defined by the vertebral spines, to the left-most point of the pulmonary arterial segment on the cardiac silhouette is measured and divided by one half of the transthoracic diameter, as suggested by Ozawa.[6]

2. A positive correlation between the "PA/chest ratio" and pulmonary arterial mean pressure was found. The correlation was exponential in character, resembling the shape of the pressure-volume curve.

3. The correlation between PA/chest ratio and pulmonary arterial mean pressure is poor in patients with left-to-right shunts and increased pulmonary blood flow.

4. In patients with mitral stenosis, in whom pulmonary blood flow varies over a relatively narrow range, the PA/chest ratio is a useful guide to the presence or absence of pulmonary vascular disease, facilitating preoperative evaluation of these patients without cardiac catheterization.

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On the Interpretation of Cancellation Experiments

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In clinical electrocardiography it has been customary to divide leads into two categories, remote and local. Remote leads have been presumed to be more or less equally sensitive to electromotive forces in different parts of the heart, whereas local leads have been considered to be more sensitive to electromotive forces in that portion of the heart nearest to the electrodes. A decade ago this commonly accepted point of view was questioned by P. W. Duchosal,[1] on the basis of studies in which voltages in unipolar chest leads were estimated with fair accuracy from vectorcardiograms recorded from remote leads. His work indicated that local leads behaved essentially as remote leads, and did not exhibit the expected "proximity" effects. Since then, after further experiments with the hearts of cats,[2] he has qualified his support of this hypothesis.

Nevertheless, others[3-5] have reasserted Duchosal's early view, on the basis of data from more sophisticated experiments, the most quantitative of which make use of Burger's concept of the lead vector.[6] When this concept is applied to special leads called "cancellation" or "null" leads, it can be shown that these leads, by proper adjustment, can be made insensitive to the effects of dipoles located at any fixed point. Experiments with these leads have demonstrated that in most cases they can be adjusted so that the output voltages are low, and some experimenters have concluded from this that the electromotive forces of the heart can be represented by a dipole located at one fixed point, and that unipolar chest leads are therefore superfluous.

This point of view has been summarized by E. Frank[3] in an exhaustive discussion of the "Fixed-Location Dipole Hypothesis." He states, ". . . it would be extremely valuable clinically to glean information concerning local regions of heart muscle that are close to an exploring precordial electrode, but this is a fleeting hope that melts in the face of experimental facts."

Many investigators have questioned this conclusion.[7-11] Morton, Romans and Brody,[11] in particular, suggest that voltages of cancellation leads will be small even if the electromotive forces of the heart cannot be represented by a

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This investigation was supported by Research Grant H-3612 from the National Heart Institute, U. S. Public Health Service, and by a research grant from the Onondaga County Heart Association, Syracuse, N. Y.

Received for publication May 13, 1959.

dipole at a fixed point. They give experimental evidence showing that one of the cancellation leads can be so adjusted that its output will have two or more zero crossings, and this, one recognizes intuitively, would tend to keep the lead voltage low. They suggest in addition that this cancellation procedure will result in a weak lead field[11-14] which would also tend to lessen the cancelled voltage.

In this paper, the work of Brody and his associates is extended in two ways. First of all, a study is made of the potentials set up in a volume conductor by time-varying dipoles located at many points within the conductor. The situation is made to simulate that of the electromotive forces of the heart in the human body. It is found that the resulting differences in potential can be made to nearly cancel one another despite the fact that the sources are by no means located at a single point. The theoretical reasons for this cancellation, which were first pointed out by Brody's group, will be discussed quantitatively in another paper. It will be shown there that if the electromotive forces of the heart were effectively located in a small part of its volume, then the cancellation ratios attained in experiments with human subjects should be much smaller than the ratios which have actually been measured and reported in the literature.

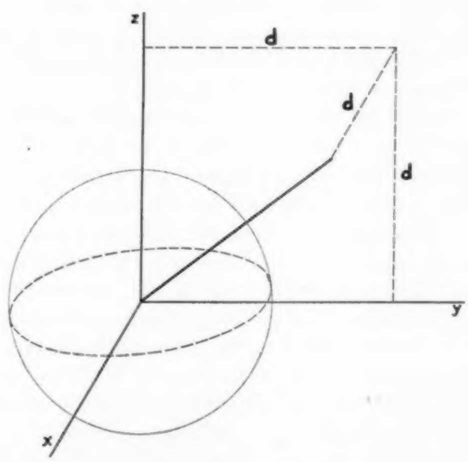

Fig. 1.—Relative orientation of the heart leads and the unipolar lead in the infinite homogeneous conductor.

THE MATHEMATICAL MODEL

The objective of the experiment was to determine, using a mathematical model of the human body and the electromotive forces of the heart, the degree of cancellation attainable in leads equivalent to the cancellation leads which have been used in experiments with human subjects.

For simplicity, the body was represented as an infinite homogeneous conductor, and the heart as a sphere. This simplification enabled the potentials in the leads to be determined by calculation, rather than by measurement. Identical results would have been obtained experimentally if the measurements had been made in a large body of water. The body, of course, is not an infinite homogeneous conductor, but it is known from studies of the body as a volume conductor[12] that the results obtained using this model will not be qualitatively in error.

The cancellation lead used was that proposed by Becking, and investigated extensively by Burger[7] and his associates. In the Becking-Burger cancellation arrangement the voltages obtained

from three leads are added together with suitably chosen weighting factors so that they equal as closely as possible the voltage of a fourth lead. The difference between these two voltages is then the "cancelled" output of the Becking-Burger lead. In the calculations reported here, the weighting factors were determined by a trial-and-error mathematical procedure.

The four leads used in making up the cancellation arrangement were the orthogonal x, y, and z "heart vector" leads, and a fourth "unipolar" lead taken between an "exploring electrode" close to the heart and another electrode at "infinity." The exploring electrode was oriented with respect to the heart and the three "heart vector" leads so that the angles between the x, y, and z axes and a line joining this electrode to the center of the heart were equal. With this arrangement an electromotive force at the center of the heart, if pointed at the exploring electrode, would produce equal positive voltages in all the heart vector leads. This orientation is illustrated in Fig. 1.

Two different configurations were used for the electromotive forces. In the first one, the electromotive forces were located at two points in the sphere, one halfway between the center of the heart and the point on the surface of the sphere closest to the exploring electrode, and the other in a similar position on the opposite side of the sphere. In the second configuration, electromotive forces were located at seven points, one at the center of the sphere, and the other six symmetrically placed about it, each two thirds* of the way from the center of the sphere to the surface. This arrangement simulates the dispersion of electromotive forces uniformly throughout the heart. The electromotive force at each point consisted of three components, one pointing parallel to the line between the sphere's center and the exploring electrode, and the other two perpendicular to the first component and to each other.

To make the calculated lead voltages similar in form to those usually encountered in electrocardiography, each of the three components of each electromotive force was made to vary in the same fashion as an electrocardiogram registered from a human subject. To this end, electrocardiograms were recorded from a variety of leads on eleven persons, using a high-speed photographic recorder. Twenty-one of the best (i.e., lowest noise) records were selected, taking no more than two from each person, and the amplitude of the deflection was carefully measured at seventeen equally spaced points in the QRS complex. The deflections at the first and last points were taken as zero. The twenty-one records used are shown in Fig. 2.

In order to assign these records to the components of the electromotive forces in a random fashion, and to insure that the magnitudes and polarities of the components were random, the following steps were taken: The measured values of the twenty-one records were placed on twenty-one cards and the cards shuffled, and the assignments made after shuffling. The measured deflections of each record were "normalized" so that they all had a peak value of 1. The magnitude and polarity of each component of each electromotive force was made random by throwing a pair of dice and multiplying all deflections of each record by the deviation of the throw from 7. Thus, a throw of 5 multiplied the record by −2, whereas a throw of 7 multiplied it by 0. Since a throw of 6 or 8 is much more likely than a throw of 2 or 12, it was only rarely that the records were multiplied by a number as large as 5.

Calculations of the voltages induced in the four leads by these dipole components were made using the standard equation for the electrical field of a dipole in infinite homogeneous conductors.

$$V = \frac{Km}{R^2} \cos \theta$$

Here V is the potential of the point in question, and θ the angle between the dipole and the line joining it to the point of measurement. The constant K is determined by the conductivity of the medium, and m by the moment of the dipole. R is the distance between the dipole and the point of measurement.

The voltages in the x, y, and z heart vector leads were proportional to the projection of the components of the electromotive forces in their direction, and not dependent on the location of the electromotive forces. The voltage at the close exploring electrode did depend on the distance

*It is probable that the heart's electromotive forces are located, on the average, slightly further out, since the centrally located cavities of the heart are electrically inactive.

between this electrode and the various electromotive forces, and proper allowance was made for this as well as for variations in the orientation of the different components of the different electromotive forces with regard to the exploring electrode. The most time-consuming and tedious part of the calculation involved determining the three weighting factors, α, β, and γ, which would make the peak excursion of

$$\Delta = \alpha x + \beta y + \gamma z - u$$

a minimum. Here Δ represents the output of the cancellation lead; x, y, and z the voltages of the heart vector leads; and u the voltages of the unipolar lead. Also calculated was P, the voltage of the exploring electrode with all the electromotive forces located at the heart's center.

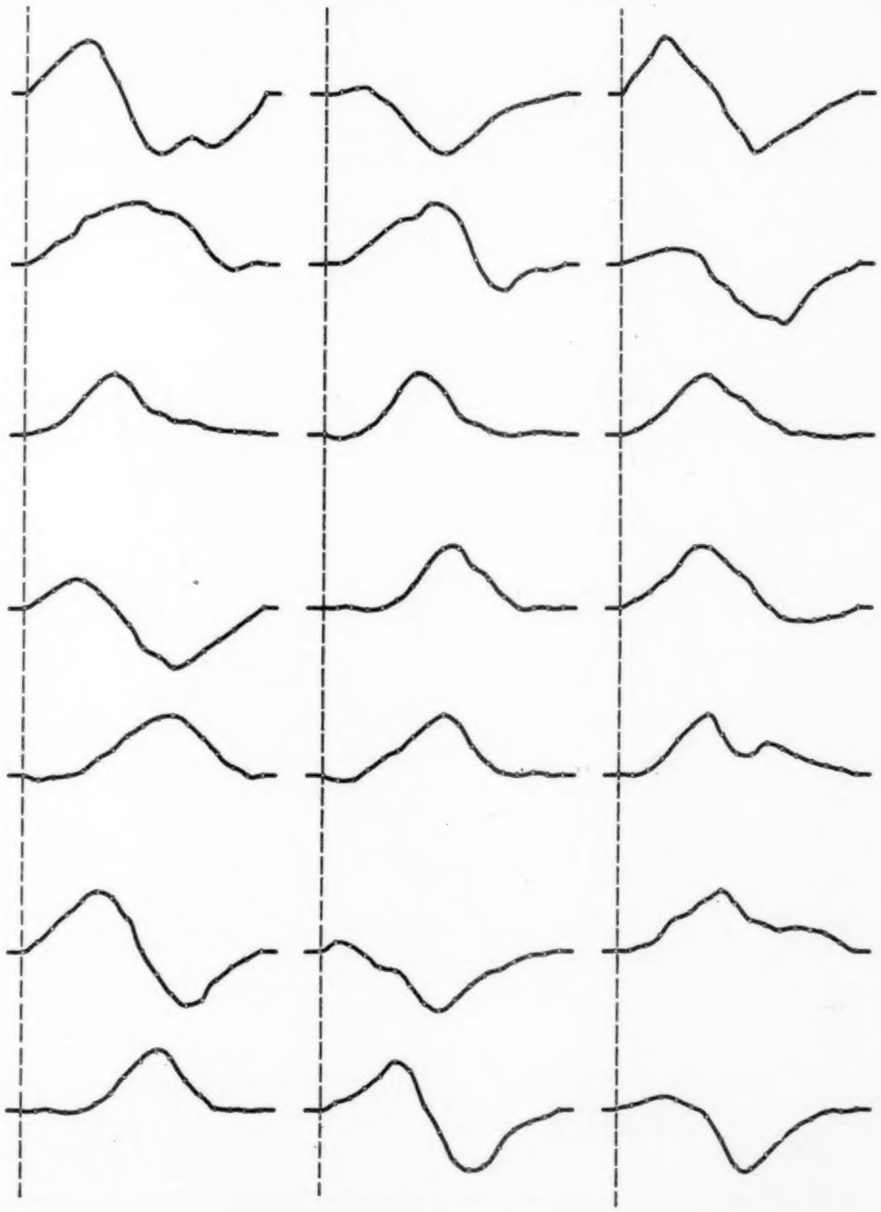

Fig. 2.—The twenty-one electrocardiographic records used to specify time variations of the three components of the heart's electromotive forces at the various points in the heart. Note that all records are "normalized" to a peak value of 1.

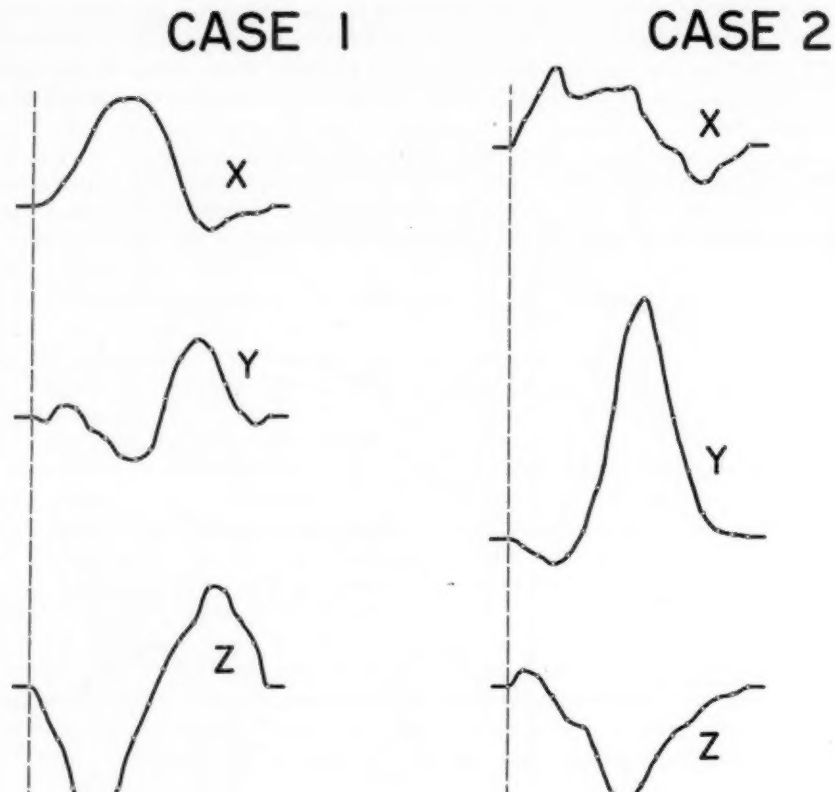

Fig. 3.—Lead voltages induced by a heart with electromotive forces at two points. The exploring electrode is one half of a heart diameter from the heart surface. For further details, see text.

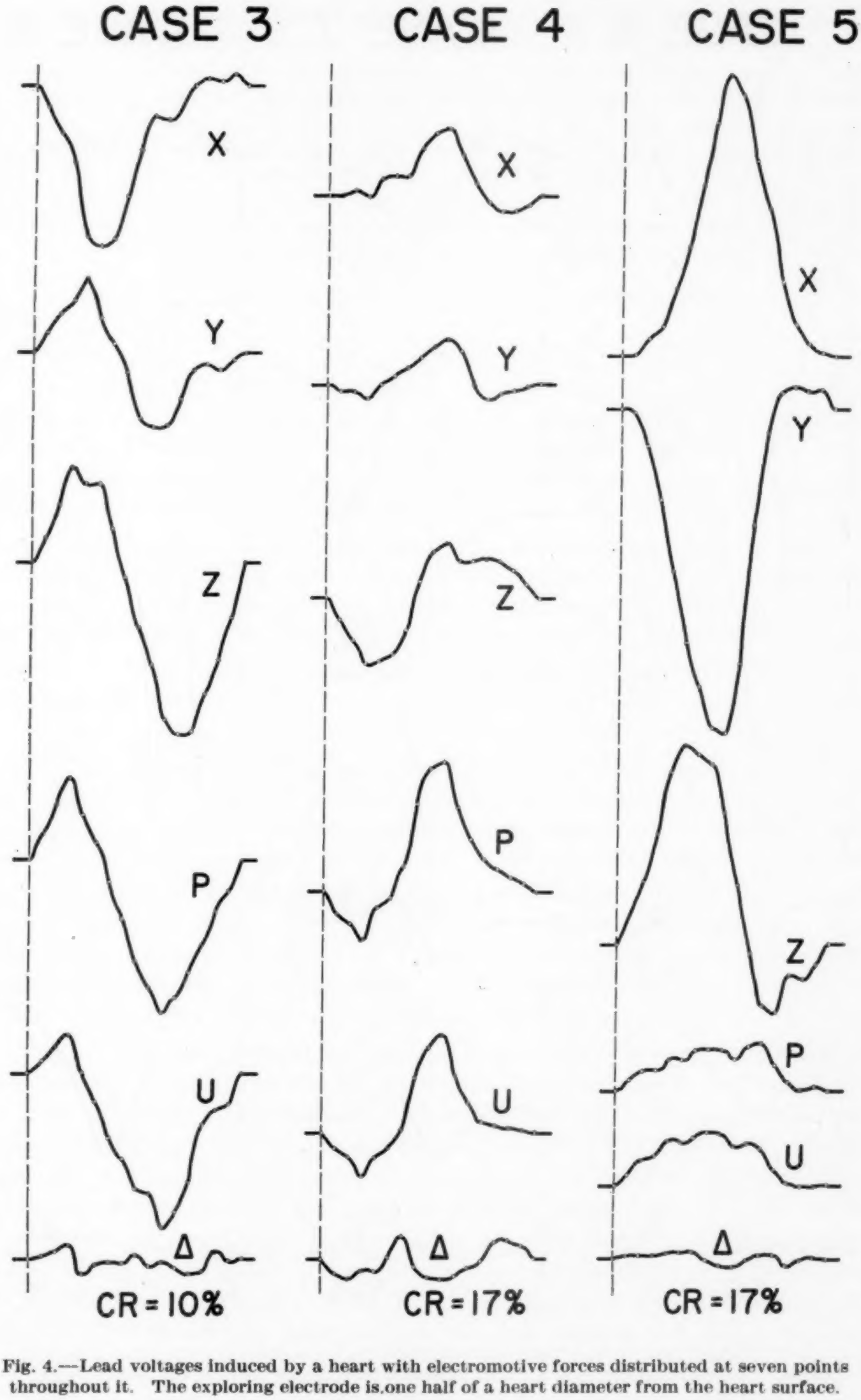

Fig. 4.—Lead voltages induced by a heart with electromotive forces distributed at seven points throughout it. The exploring electrode is one half of a heart diameter from the heart surface.

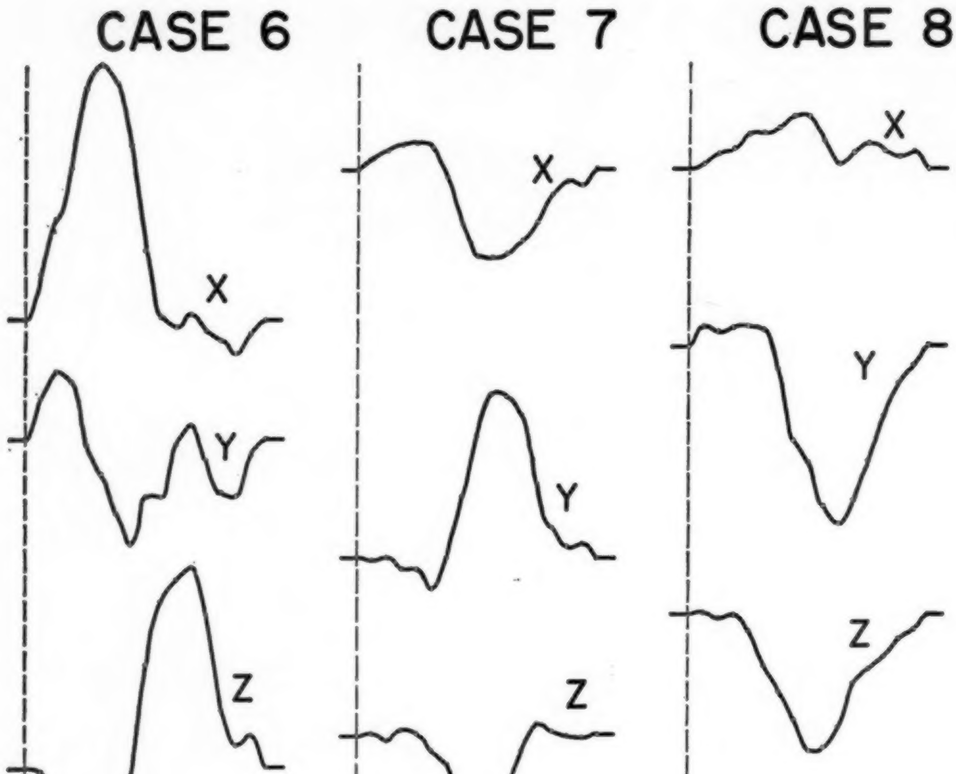

Fig. 5.—Lead voltages induced by a heart with electromotive forces distributed at seven points throughout it. The exploring electrode is one and one-half heart diameters from the heart surface.

These calculations were done for a total of eight cases. In the first two cases (Cases 1 and 2) the two-point configuration of electromotive forces was used, with the exploring electrode one half of the heart diameter from the surface. In Cases 3-5 and 6-8 the seven-point configuration of electromotive forces was used, with the exploring electrode one-half and three-halves heart diameters from its surface, respectively. In each case the assignment of the ECG records to the components of the electromotive forces was made anew by reshuffling the cards, and the throwing of the dice was repeated. It should be emphasized that *no cases were discarded.* The data given in the next section represent every case which has been investigated in whole or in part. The calculations involved were straightforward but lengthy, requiring from one to two weeks of full-time work per case. It is for this reason that the calculations have not been repeated using a wider variety of lead locations, etc.

RESULTS

The results obtained in the two-point configuration of electromotive forces, with the relatively close exploring electrode, are shown in Fig. 3. Fig. 4 shows the seven-point configuration with the close exploring electrode, and Fig. 5 shows the seven-point configuration with the relatively remote exploring electrode. Each of the synthetic electrocardiograms shown has been drawn with a French curve to pass through the seventeen points representing the calculated deflections of the lead voltages. To indicate the location of these points they are shown in all of the complexes in the illustrations. The cancellation ratio for each case is shown along with the figure. It is here defined as the ratio of the peak deflection of the cancelled voltage, Δ, to the peak deflection of the voltage u in the unipolar lead.

It is not necessary to say a great deal about the results, since they speak for themselves. They show that good cancellation is attained regardless of the fact that electromotive forces exist simultaneously at a number of points dispersed throughout the "heart." Good cancellation is achieved even when the exploring electrode is in close proximity to the heart. The results also show a substantial difference between the voltage of the exploring electrode and the voltage which it would have if all of the electromotive forces were located at the center of the "heart." This difference reflects the greater influence of the nearer dipoles, and the lesser influence of the more remote ones. It is evident that "proximity potentials" may exist in human subjects, even when good cancellation occurs.

The results are in reasonably good agreement with those expected from the theory presented in the next paper. For example, where the exploring electrode is in close proximity to the heart, the predicted cancellation ratio is 13 per cent, whereas the average of the five cases investigated here is 15 per cent. The predicted cancellation for the remote electrode is 7 per cent, as compared to an average of 13 per cent over the three cases investigated here. We believe that the latter figure would have been reduced substantially if a larger number of cases had been investigated. It is clear that good cancellation can be achieved with the electromotive forces of the heart dispersed throughout its volume, and that proximity effects can exist even when good cancellation exists. In fact, the theory presented in the next paper shows that if the electromotive forces were located in a sphere one centimeter in diameter, or about one tenth of the diameter of the heart, as has been suggested by one proponent of the fixed-dipole

theory,[3] the cancellation ratios should be less than one per cent. This is not found to be the case in actual cancellation experiments. The measured cancellation ratios are actually of the same order of magnitude as the cancellation ratios obtained with the mathematical model here, in which the electromotive forces are distributed over the entire heart. This indicates strongly that in normal human subjects the electromotive forces of the heart are distributed throughout its entire volume, and are not located either actually or effectively within a small region of it.

CONCLUSIONS

Study of a mathematical model which simulates a human body and has a number of time-varying electromotive forces distributed throughout its "heart" shows that good cancellation is achieved regardless of the dispersion of these electromotive forces. It is also found that the potential of an electrode close to the heart differs substantially from the projection of the heart vector in its direction. These results are in reasonably good quantitative agreement with theory, and indicate strongly that the electromotive forces of the heart cannot be represented by a dipole at a fixed point, and that information exists in precordial and esophageal leads which cannot be extracted from vectorcardiographic data.

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Work Capacity of the Left Ventricle Following Ligation of the Coronary Artery

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Although a number of studies have been made of the changes in the dynamics of the ventricles following coronary artery occlusion,[1-4] there have been few attempts to evaluate the maximum contractile force of the myocardium either at the time of infarction or during the period of recovery. Most of the studies made during the acute stage of myocardial infarction describe resting levels of various parameters,[5-10] whereas performance estimates made during convalescence have been based upon indirect measurements of the work capacity, such as exercise tolerance.[11-15] In the present study, the heart-lung preparation was used to measure the work capacity of the dog heart, both immediately after standard ligation of the coronary artery and at selected intervals up to 133 days thereafter.

METHOD

Mongrel dogs weighing 9.8 to 13.2 kilograms were anesthetized with Nembutal, 20 mg./Kg., and ventilated with a mechanical respirator using oxygen.

In the acute experiments the sternum was split, the pericardium widely incised, and the origin of the left anterior descending coronary artery exposed by blunt dissection. Two ligatures were passed under the artery distal to the point of origin of the septal branch. Following this the heart-lung preparation described elsewhere[16] was established. After a 15-minute period of stabilization, the ligatures around the left anterior descending coronary artery were drawn tight and the artery divided between them. In no case was flow through the septal branch interrupted. After another 15-minute period of stabilization, the work capacity of the heart was determined as described below.

For the experiments involving longer survival after ligation of the coronary artery, the chest was entered through the fourth left intercostal space under sterile conditions, the pericardium was widely incised, and the left anterior descending branch was doubly ligated and divided in a manner similar to that described above. The chest was closed in the routine manner, and no attempt was made to close the pericardium. Animals which survived the ligation were given one injection of 600,000 units of penicillin and confined thereafter to standard cages. At intervals between 7 and 133 days, heart-lung preparations were made of these animals, and their cardiac work capacities determined.

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Received for publication June 1, 1959.
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Measurement of cardiac work capacity was as follows: The inflow load was gradually increased at 1 to 2-minute intervals by increments of approximately 100 ml. while the mean ejection pressure was maintained in the range of 100 to 120 mm. Hg. The inflow increments were reflected by elevations in the left atrial mean pressure. Eventually, further increases in the inflow were rejected, and the atrial pressure climbed rapidly to the level of the reservoir. The blood temperature was maintained at 37°C. All measurements were completed within an hour of establishment of the heart-lung preparation.

Arterial blood pressure was measured by Statham strain gauge manometer and Sanborn recorder. Atrial pressures were measured with saline manometers via polyethylene catheters. The left ventricular output was measured directly. Mean ejection pressure was obtained from integration of pressure tracings. Calculation of the work of the left ventricle was by standard formulae. Ventricular performance curves were constructed from cardiac work and left atrial mean pressure data. The diagnosis of acute myocardial infarction was substantiated by electrocardiography immediately after ligation of the coronary artery, by S-GOT changes in the ensuing several days, and was confirmed by autopsy, histologic study, and injection with vinyl acetate.

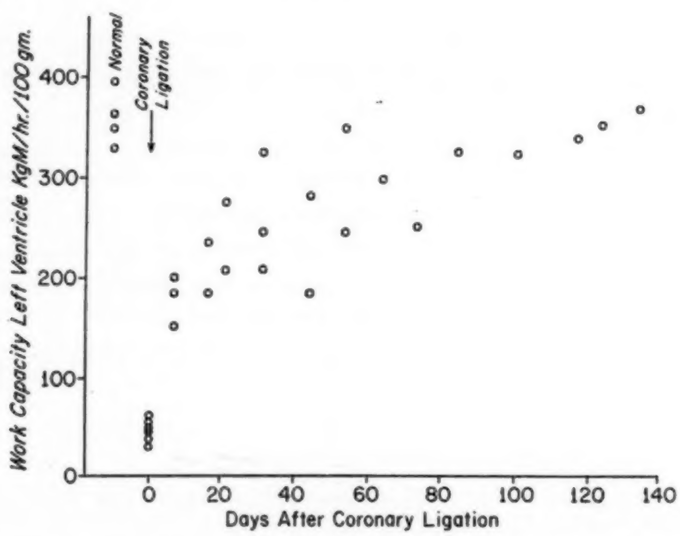

Fig. 1.—Work capacity of the left ventricle after ligation of the left anterior descending coronary artery.

RESULTS

The cardiac work capacity of four normal dogs was found to range from 325 to 390 Kg.M./hr./100 Gm. of heart weight, and the maximum stroke work from 38.1 to 42.2 Gm.M./hr./100 Gm. of heart weight. The limit of the work capacity was quite sharp; further increases in inflow resulted in elevated left atrial pressures without concomitant increases in left ventricular outflow (Fig. 3). The work capacity of the four control experiments is plotted in Fig. 1, and stroke work data are included in Fig. 2.

Measurement of the work capacity immediately after ligation of the coronary artery was attempted in 12 animals. In two of these the heart immediately became adynamic, dilated progressively, and the cardiac output rapidly fell to zero. An additional four animals developed ventricular fibrillation within 3 minutes after ligation. No data were obtained from these six experiments. In

the six remaining dogs, transient arrhythmias and hypodynamic beats were observed, but these subsided during the brief period of stabilization.

The work capacity of the hearts of these six dogs was found to range from 24.5 to 56.2 Kg.M./hr./100 Gm. of heart weight, and averaged 41.8 Kg.M./hr./100 Gm. The maximum stroke work ranged from 3.3 to 9.0 Gm.M./100 Gm. Data from these experiments are included in Fig. 3.

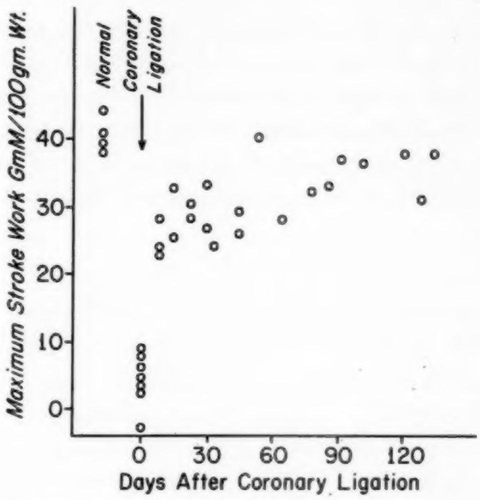

Fig. 2.—Maximum stroke work of the left ventricle after ligation of the left anterior descending coronary artery.

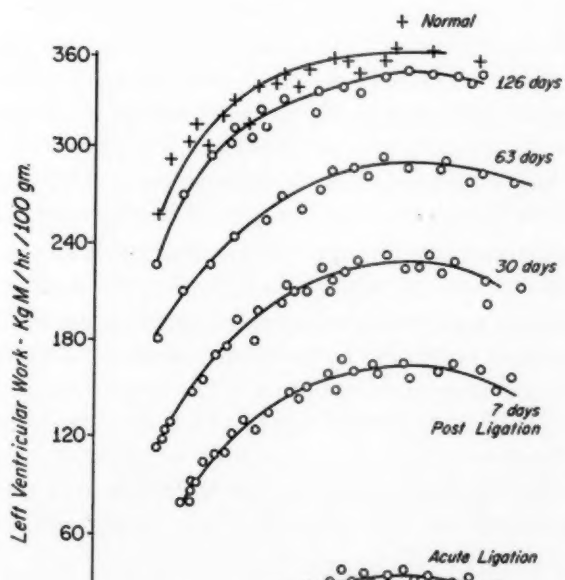

Fig. 3.—Left ventricular function curves at various intervals after ligation of the left anterior descending coronary artery.

Of 59 dogs which underwent ligation of the coronary artery, 21 survived to be utilized in the long-term study. The work capacity of three of these was determined 7 days after ligation; two were studied at 14 days, two at 21 days, three at 30 days, and two each at 40 and 60 days. An additional seven dogs were studied at random intervals between 60 and 133 days.

The work capacity of the three hearts in which determinations were made 7 days after ligation averaged 165 Kg.M./hr./100 Gm., slightly less than 50 per cent of the control level. At 30 days the work capacity averaged 240 Kg.M./hr./100 Gm., and by 60 days it had returned to approximately 300 Kg.M./hr./100 Gm. The data obtained in five dogs surviving 90 days or more after ligation were comparable to the data obtained from control animals. The maximum stroke work followed a similar pattern of recovery. The data are plotted in Figs. 1 and 2, and representative experiments are included in Fig. 3.

DISCUSSION

The effect of restriction of coronary flow on left ventricular performance was investigated by Sarnoff and associates.[17,18] Using a different preparation this group showed that even mild restriction of coronary flow resulted in a diminution of left ventricular stroke work, whereas moderate restriction of coronary flow, without infarction, was followed by a marked decrease. In the present study, acute ligation of the coronary artery was followed immediately by a precipitous drop in cardiac work capacity and maximum stroke work; none of these hearts was capable of 25 per cent of the work observed in the control group.

The reduction in ventricular performance immediately after ligation has been attributed to three factors[3]: deletion of contracting muscle tissue, paradoxical distention of the infarcted zone, and arrhythmias. The first of these was probably of primary significance in the present study, since the autopsy studies indicated that the technique selected resulted in infarction of approximately 35 per cent of the left ventricle. Paradoxical distention was also grossly visible, but arrhythmias were not present at the time data were obtained.

Within a week after ligation the work capacity had returned to approximately 50 per cent of the control level. By this time the infarcted area was undergoing organization, and was grossly more rigid and less susceptible to paradoxical motion. The functional status of the periphery of the infarcted area was difficult to evaluate. It is a common observation that the area of cyanosis which develops immediately after ligation is much larger than the resulting area of fibrosis. While collateral development is not sufficient to prevent central infarction, it would appear that muscle fibers in the border are made only temporarily ischemic by the ligation, and later are able to resume function, perhaps being supplied by a new source.

Between 60 and 90 days after ligation the work capacity was observed to approach control levels, whereas data obtained from experiments performed over 90 days after coronary ligation were essentially similar to the data obtained from control animals. By this time the infarcted region had been replaced by a thin but inelastic scar which supported the maximum pressure and volume loads

without evidence of dilation. Inasmuch as this fibrous tissue replaced an area of contracting myocardium, but was itself noncontractile, it was postulated that there had been an increase in the force generated by the remaining viable muscle fibers.

There are a number of reasons why the prompt and complete recovery of work capacity noted in these experiments cannot be expected to occur in the patient who has survived a clinical episode of myocardial infarction of similar extent: the animals used in this study had no evidence of underlying metabolic or vascular disease; the experimental lesions were limited to a single large coronary artery, without involvement of other rami; the relative ease and rapidity with which collaterals develop in this species is well known; the conditions of the experiment were controlled more rigidly than is possible with patients. Even under these more favorable conditions, there was an immediate drastic reduction in the cardiac reserve; the maximum cardiac effort was hardly sufficient to supply basal requirements, and any additional load, however slight, precipitated failure. These observations would favor a strict regimen of rest following acute myocardial infarction. Similarly, the recovery of less than 50 per cent of the work capacity within 2 weeks augurs against a program of early ambulation. Finally, the essentially complete recovery such as was observed in animals which had been at rest for 90 days or more can be expected to occur similarly in patients only when the occlusion represents an isolated lesion, and when there is no generalized coronary sclerosis to prevent a compensatory increase in the contractile force of the remaining myocardial fibers.

SUMMARY

The canine heart-lung preparation was used to measure the work capacity of the left ventricle at various intervals after standard ligation of the left anterior descending coronary artery. Immediately after ligation, the work capacity dropped to less than 20 per cent of the control level. After 1 week, the left ventricular work capacity returned to nearly 50 per cent of the control value. Data obtained at frequent intervals thereafter showed gradual return to normal, and those animals which were allowed to survive 90 days or more after ligation regained essentially normal left ventricular work capacity. Left ventricular stroke work followed a similar pattern.

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Cardiac Effects of Intracoronary Arterial Injections of Various Roentgenographic Contrast Media

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The causes of death following the administration of a contrast substance for the purpose of angiocardiography and pyelography have not been fully ascertained. In the 6,824 instances of angiocardiography collected by Dotter and Steinberg,[1] 26 deaths were reported; the most common form of death was respiratory arrest immediately or shortly following the injection of a contrast substance. Others[2,3] ascribed the fatal outcome to "allergic sensitivity," cardiac arrest, and acute heart failure. This problem has stimulated considerable experimental work on the systemic effects of the different contrast media used for angiography. However, most of the studies[3-5] were confined to a specific radiopaque dye, and no direct and systematic comparison of the cardiovascular effects of the various contrast substances was made. Furthermore, the results obtained were equivocal because the only cardiovascular observations made were those on the blood pressure and the electrocardiogram.

By utilizing various procedures which have made it possible to catheterize and inject drugs into the coronary artery while simultaneously measuring coronary blood flow and myocardial contractility,[6] we have studied the direct cardiac effects of the different contrast media on coronary blood flow, myocardial contractility, and the electrocardiogram. The method of coronary artery catheterization permits introduction of small amounts of radiopaque dye material into the coronary circulation for the purpose of eliciting local cardiac response without evoking systemic effects elsewhere in the circulation. In this way we hope to

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Supported by a grant-in-aid from the American Heart Association.

This work was done during Dr. Guzman's tenure of a Research Fellowship of the American Heart Association, Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pa.

Received for publication June 15, 1959.

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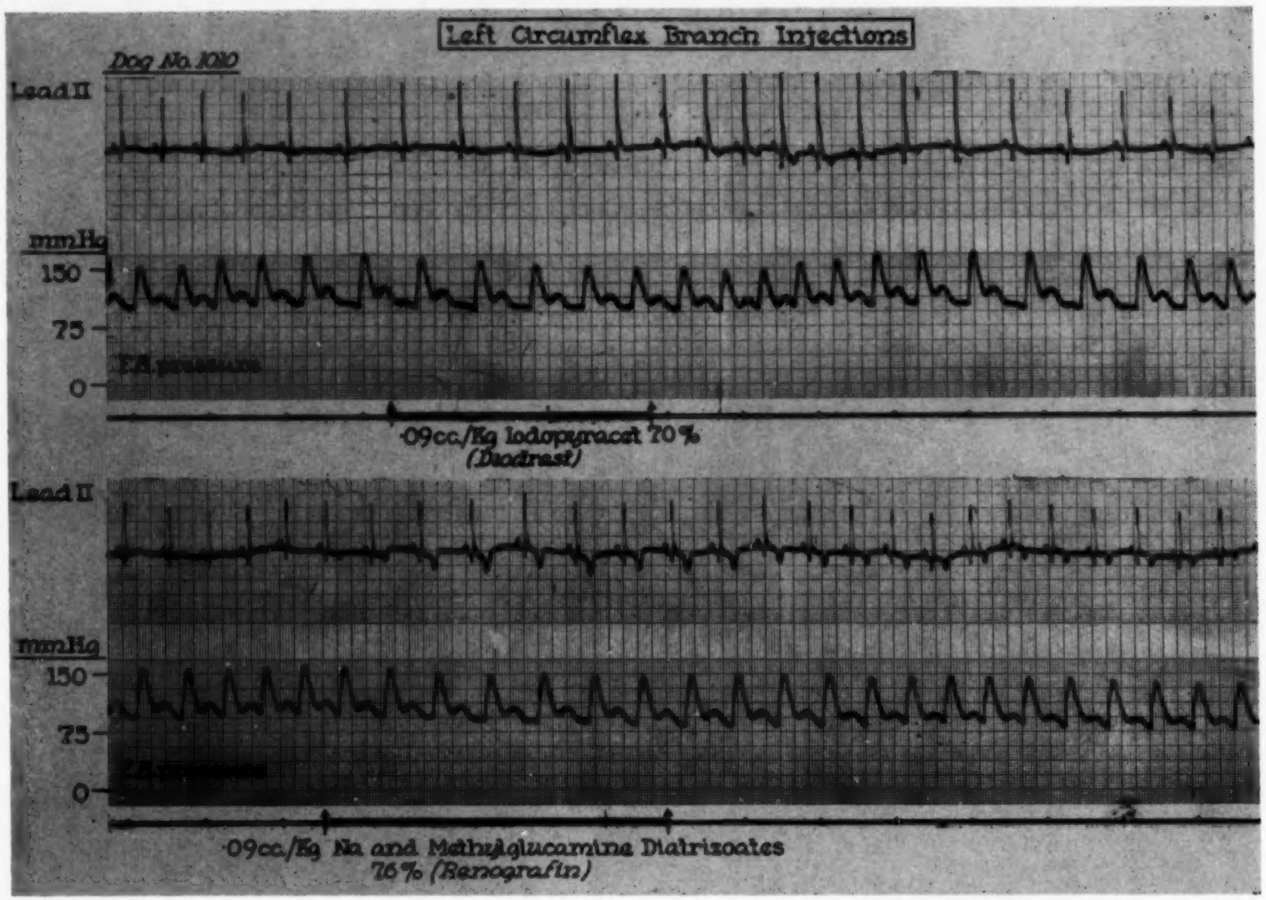

Fig. 1.—Effects on the electrocardiogram and systemic blood pressure of the injection of dye into the left circumflex branch. Note the slight inversion of the T wave of the ECG and drop in systemic blood pressure following intracoronary injections of Diodrast and Renografin.

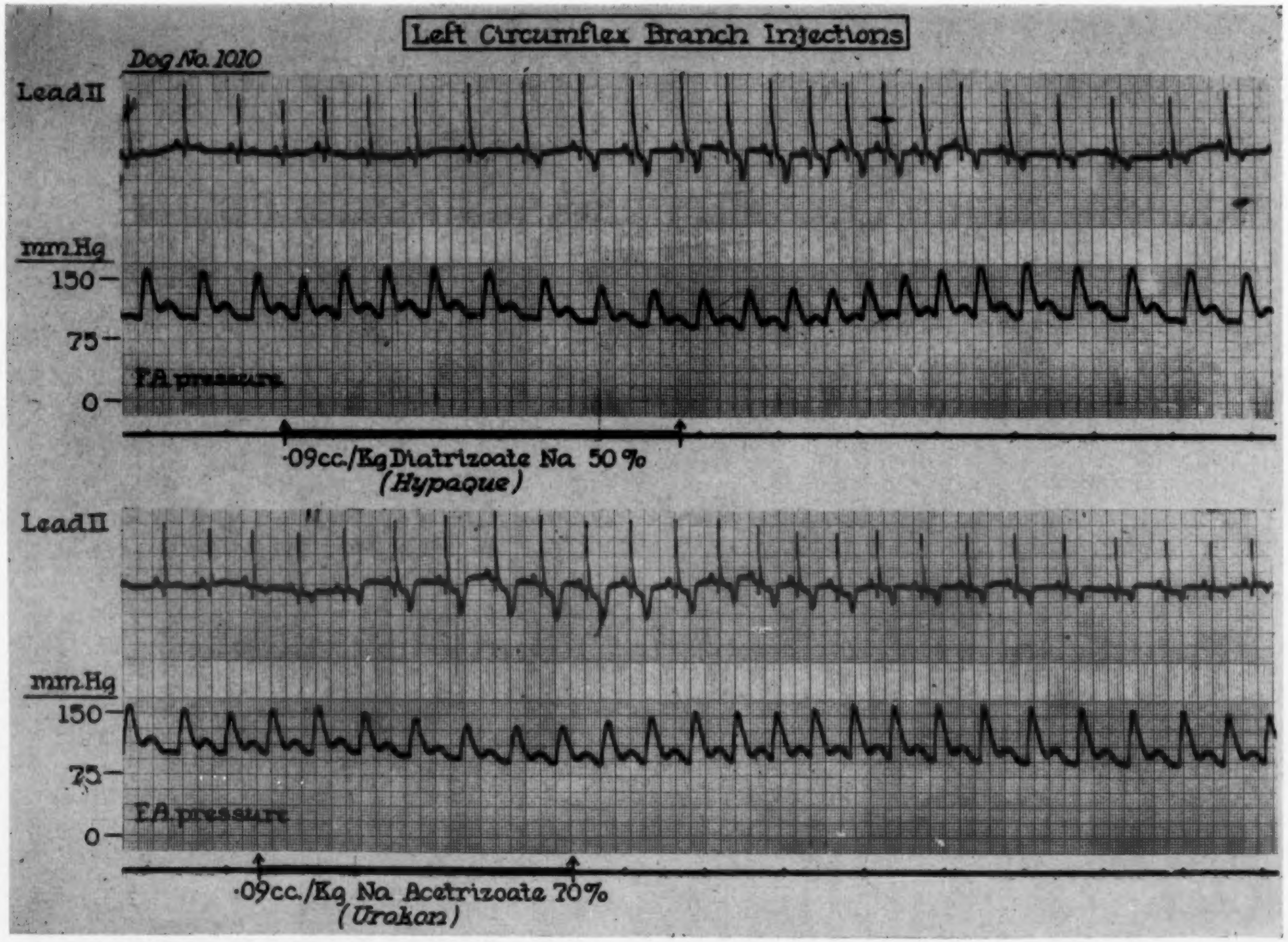

Fig. 2.—Effects on the electrocardiogram and systemic blood pressure of the injection of dye into the left circumflex branch. The changes in the T wave of the ECG and the drop in systemic blood pressure are more profound following injections of Hypaque and Urokon than they are following injections of Diodrast and Renografin (Fig. 1).

gain insight into some of the possible mechanisms responsible for the "cardiac" death following angiocardiography. Furthermore, the results concerning the comparative "cardio-toxic" effects of the different commonly used radiopaque substances would appear to be of considerable interest, especially because of their extensive use in cardiovascular roentgenography, including coronary arteriography in man.[7,8]

METHODS

The studies were performed on 22 normal adult mongrel dogs weighing 20 to 25 kilograms, under light anesthesia by morphine-chloralose (70 mg./Kg.) or a combination of Dial-urethane and pentobarbital sodium (100 and 400 mg./ml., respectively) given intravenously (0.25 ml./Kg.) after a previous subcutaneous injection of morphine (3 mg./Kg.). Systemic blood pressure was recorded from the femoral artery, using a Statham strain gauge and a direct-writing Sanborn Poly-Viso recorder. The electrocardiogram was continuously monitored, in the same recorder, using a standard lead II and/or a precordial lead (V_3). Myocardial contractility was measured using a Walton strain gauge[9] sutured directly to the exposed surface of the left ventricle in the area supplied by the coronary artery into which injections were made. The myocardiogram was recorded in the same multichannel Sanborn recorder. Coronary blood flow was measured as coronary sinus venous outflow, and quantitative measurements were obtained by timing a measured blood volume. This was accomplished by catheterization of the coronary sinus, using a modified Morawitz cannula which was inserted via the external jugular vein under fluoroscopic guidance. The catheter was provided with multiple openings at the tip and an inflatable balloon for securing it in the coronary sinus. The various branches of the coronary arteries were catheterized under fluoroscopic guidance by way of the carotid artery.[6] The chest remained intact in all experiments except those involving the measurement of myocardial contractility by the Walton myocardiograph.

The effects following intracoronary arterial injections (0.025 to 0.25 c.c./Kg.) of Diodrast (iodopyracet) 70%, Urokon (sodium acetrizoate) 70%, Hypaque (sodium diatrizoate) 50%, Renografin (sodium and methylglucamine diatrizoates) 76%, and Cardiografin (methylglucamine diatrizoate) 85%, were studied on coronary blood flow, myocardial contractility, and the electrocardiogram. The sequence of injections was varied in each experiment in order to avoid the influence of a previous injection on the effect of each radiopaque material.

RESULTS

Effects on the Electrocardiogram.—The electrocardiographic changes following intracoronary injections of the different radiopaque substances were studied in 22 dogs (12 intact-chest and 10 open-chest preparations). The electrocardiographic changes (Figs. 1, 2, and 3) consisted of flattening or inversion of a previously upright T wave, occasionally accompanied by ST depression. A comparison of similar doses of the different contrast substances indicates that Diodrast, Renografin, and Cardiografin elicit minimal to moderate ST-T wave changes as compared to Hypaque and Urokon. Urokon appeared to be the most toxic of the group, since it often produced ventricular tachycardia, as seen in Fig. 4. Furthermore, ventricular fibrillation developed in 6 of the 22 dogs studied during intracoronary arterial injection of Urokon (0.25 c.c./Kg., 70%) and in 2 dogs after intracoronary injection of Hypaque (0.25 c.c./Kg., 50%), whereas comparative doses of Diodrast (70%), Renografin (76%), and Cardiografin (85%) did not produce this fatal outcome.

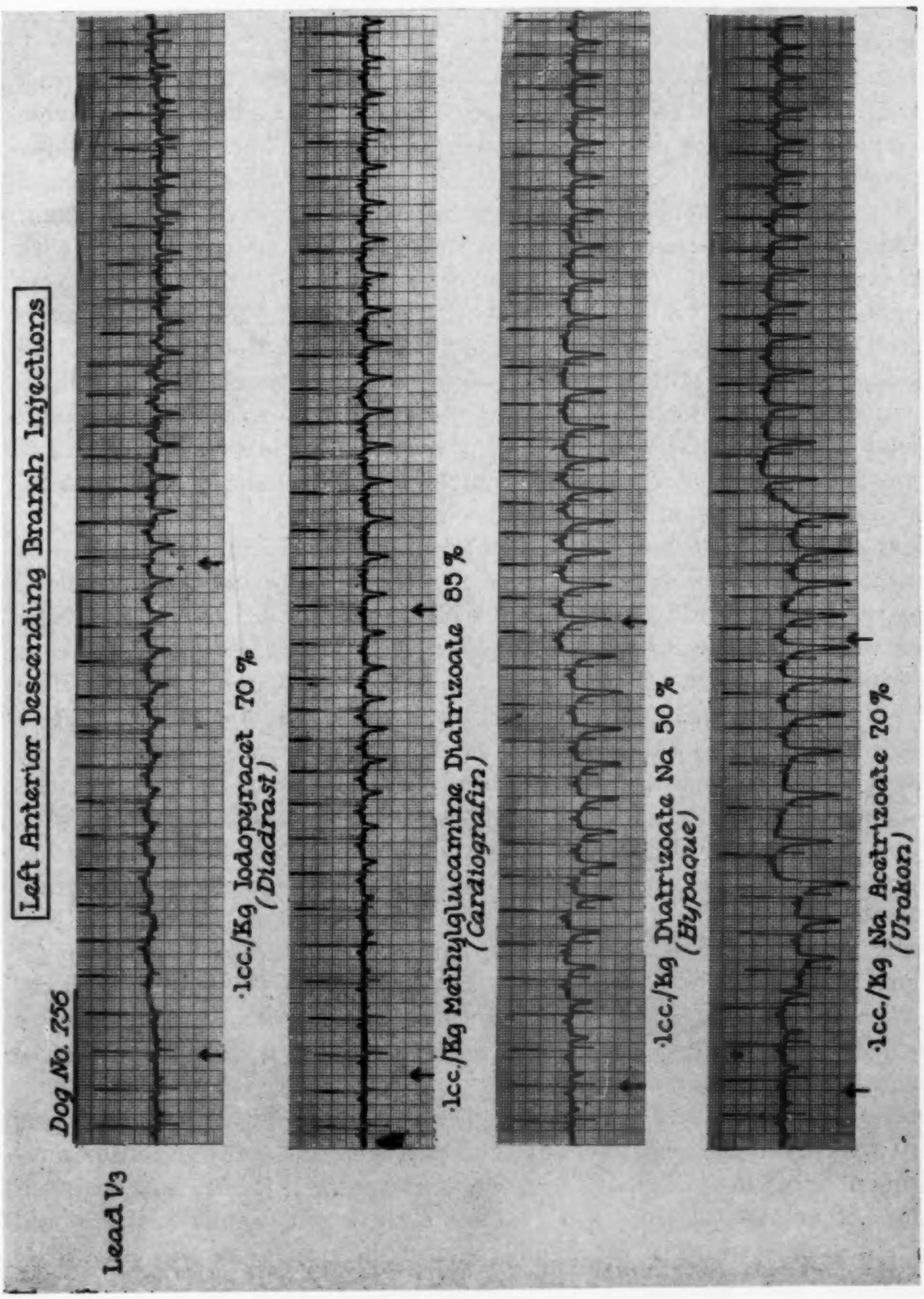

Fig. 3.—Effects on the ECG of the various radiopaque dyes injected into the left anterior descending branch. Note the profound changes of the T wave following injections of Hypaque and Urokon. Injections of Diodrast and Cardiografin in the same animal resulted in a relatively milder change in the T wave of the ECG.

All the radiopaque substances studied elicited a slight and transient increase in heart rate accompanied by a fall in blood pressure following coronary arterial injection. Urokon, however, on many occasions produced transient A-V heart block. This effect was not abolished by bilateral vagotomy, but it disappeared after atropine.

Effects on Myocardial Contractility.—The effects of the different contrast media on myocardial contractility were studied in 10 dogs, each animal receiving 2 to 4 injections of the material (0.05 c.c. to 0.25 c.c./Kg). The responses following intracoronary arterial injections of the various dyes are shown in Figs. 5 and 6. The degree of myocardial depression was most marked and persistent with Urokon (average decrease of 70 per cent of control) and least marked with Diodrast (average decrease of 15 per cent of control). The depressant effects of Hypaque, Renografin, and Cardiografin were of about the same degree, averaging about 35 per cent of control. In small doses (0.025 to 0.05 c.c./Kg.) all of the radiopaque dyes studied, except Urokon, showed a stimulant effect following recovery from depression. This stimulant effect was especially prominent after injections of Diodrast (Fig. 6). Recovery from the depressant effects of the various contrast substances was complete with all media except Urokon, in which case the depressant effect often persisted.

Effects on Coronary Blood Flow.—A total of 48 observations in 5 dogs was made on the effects of intracoronary contrast injections on coronary blood flow. Each dog received 2 to 4 injections of each of the dyes (0.025 to 0.25 c.c./Kg). Injections were given only when coronary blood flow varied less than 5 per cent over a period of 5 minutes. Immediately following the response, sufficient time was allowed for the coronary blood flow to return to the preinjection rate. The results indicate that all of the contrast media increased coronary blood flow, averaging a 60 per cent increase from the control. The increase in coronary sinus outflow coincided with the changes in the electrocardiogram and myocardial contraction. Diodrast produced the greatest and most lasting effect, the increase in coronary blood flow persisting even after the effects on the electrocardiogram had returned to normal.

Effects on Systemic Blood Pressure.—Intracoronary arterial injections of the various contrast media caused a drop in systemic blood pressure which coincided with the electrocardiographic changes. The degree of fall in pressure (ranging from 10 to 80 mm. Hg systolic pressure) appeared to parallel the degree of change in the T wave.

Effect of Repetition of Injection.—Each animal received 2 to 4 injections (coronary arterial) of each dye studied. The cardiac effects in the various parameters studied diminished following repeated injections. Thus, although an initial dose of any of the dyes will produce electrocardiographic changes and cardiac depression, a third or fourth injection of the same dose will elicit little or no response.

DISCUSSION

The results of these experiments indicate that Urokon, Hypaque, Cardiografin, Renografin, and Diodrast (listed in the descending order of effectiveness)

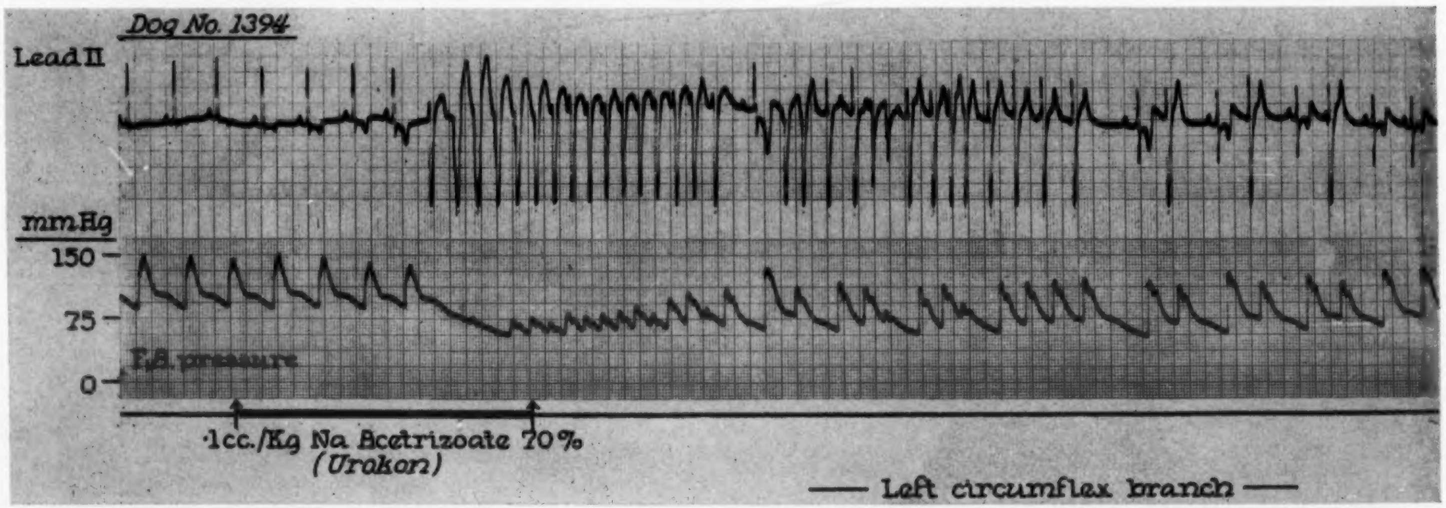

Fig. 4.—Injections of Urokon into the left circumflex branch. Note the ventricular tachycardia and drop in systemic blood pressure following intracoronary injection of Urokon.

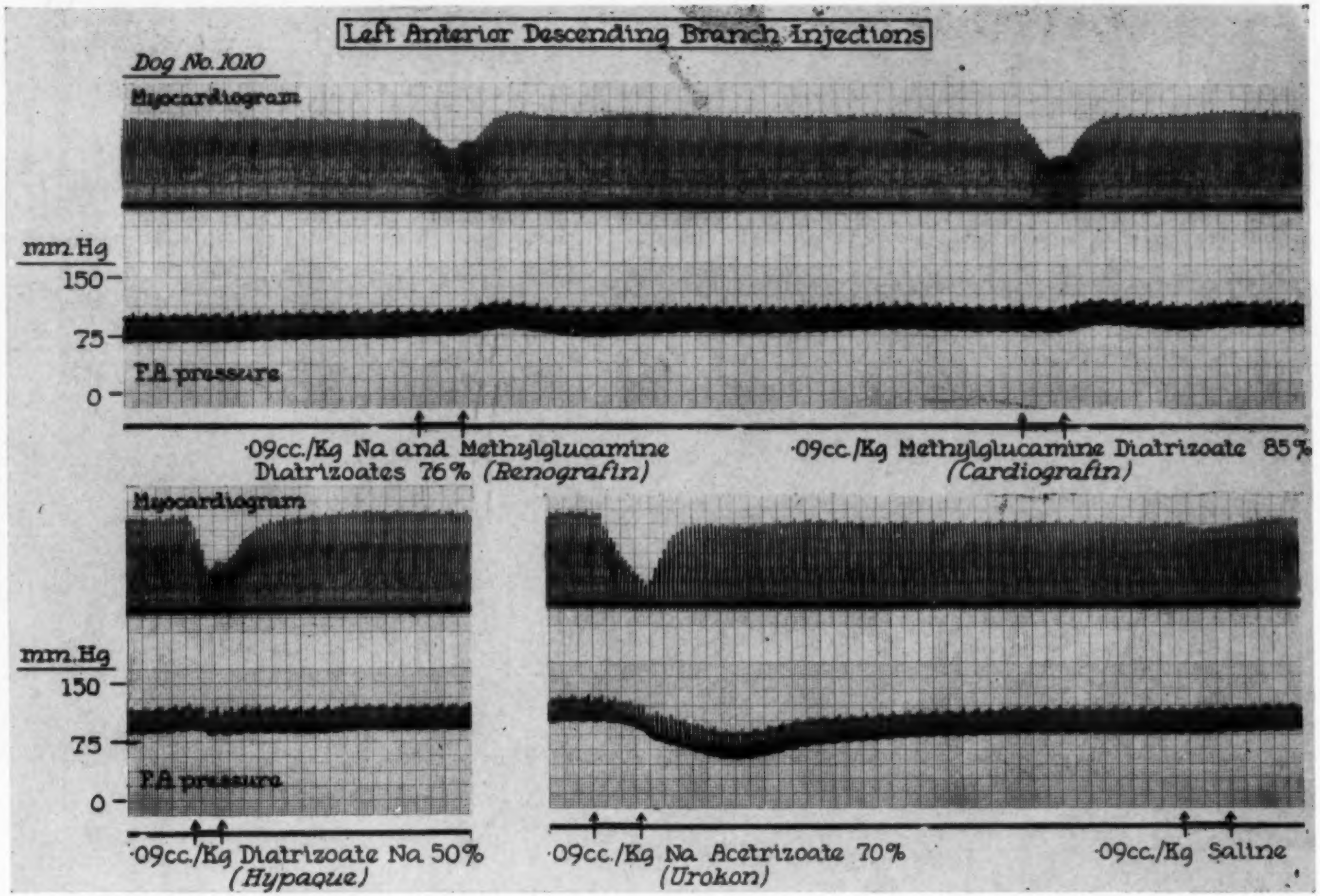

Fig. 5.—Effects on myocardial contractility and systemic blood pressure of the injection of the various radiopaque dyes into the left anterior descending branch. All of the contrast media depressed the contractile force of the heart. The effects were most pronounced with Urokon, the myocardial depression being accompanied by a drop in systemic blood pressure.

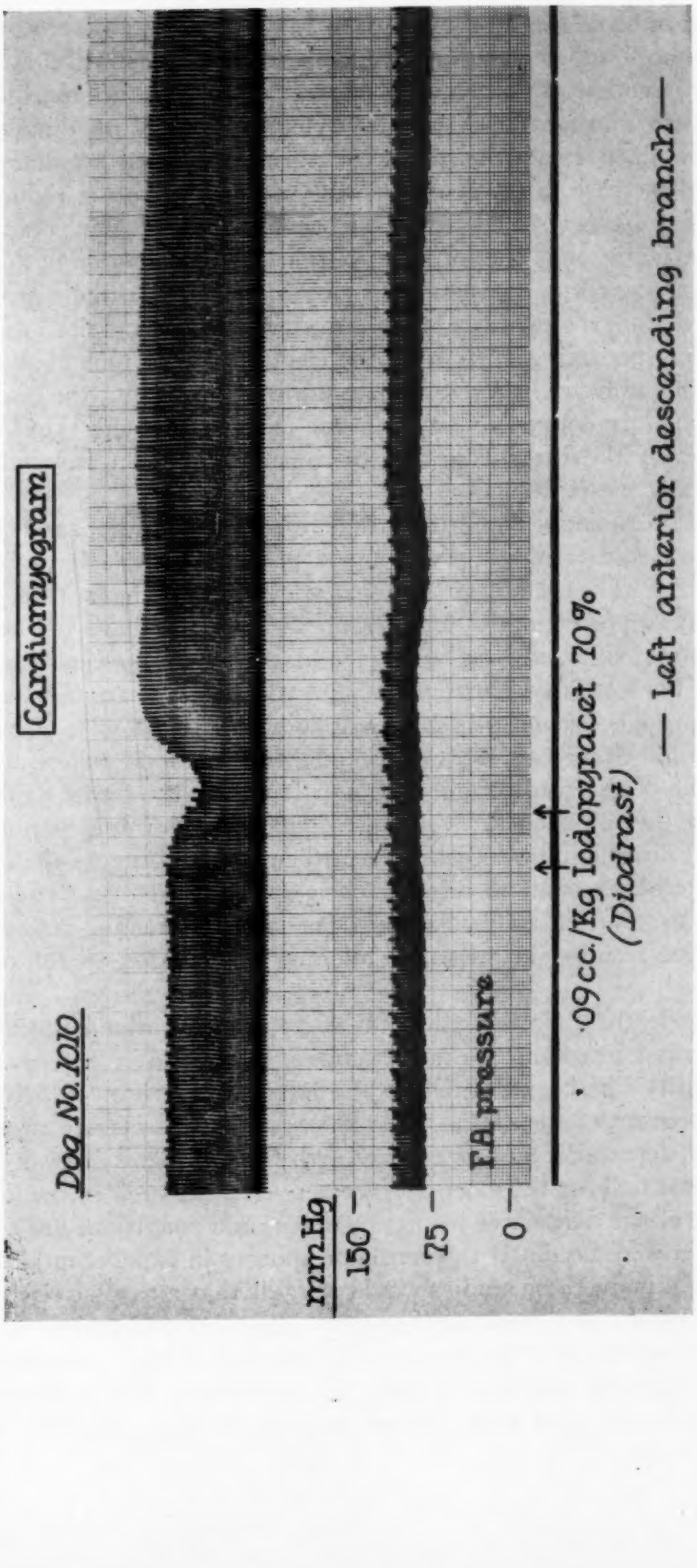

Fig. 6.—Effects on myocardial contractility and systemic blood pressure of the injection of Diodrast into the left anterior descending branch. There is a moderate depression of the contractile force followed by a moderate increase in myocardial contractility following Diodrast injection.

produced cardiac arrhythmias and ST-T wave changes in the electrocardiogram and depressed the contractile force of the heart following intracoronary arterial injections. The ECG changes were usually accompanied by a fall in blood pressure and appeared to be related to the degree of ST-T change.

All the radiopaque substances studied increased coronary blood flow following intracoronary injections. The increase in coronary blood flow coincided with the changes in myocardial contractility and the electrocardiogram. Since arterial blood pressure remained steady or decreased during increased coronary blood flow, the observed increase in coronary blood flow resulted from a reduction in coronary vascular resistance. This increase in coronary blood flow could be the result of an actual dilatation of the coronary vessels and/or reduction of the extravascular support of the coronary vessels (in view of the myocardial depression). Diodrast produced the greatest increase and most lasting effect, the increase in coronary blood flow persisting even after the electrocardiographic changes and contractile force of the heart had returned to normal, suggesting the possibility of active dilatation of the coronary vascular bed. These cardiac effects of Diodrast were also observed by Weatherall[10] in his experiments employing isolated rabbit heart and heart-lung preparations.

The effects of intravenous and intracardiac injections of radiopaque contrast substances on the electrocardiogram and blood pressure in man have been reported previously.[7,11] These changes consist of an increase in heart rate, ectopic arrhythmias, ST-T wave changes, and a drop in blood pressure following injection of the contrast substance. The drop in blood pressure varied from a few millimeters to an unrecordable pressure (using a pressure cuff around the arm). This fall in pressure has been ascribed to peripheral vasodilation.[10] Our studies indicate that similar electrocardiographic changes were found following intracoronary injections of the contrast media. Furthermore, the direct cardiac depression following the injection of dye could significantly lower systemic blood pressure. The fatalities in our studies were cardiac deaths, because the doses of contrast media were too small to directly elicit systemic effects. The cardiac deaths were due to ventricular fibrillation. It is also interesting to note that repetitive injections resulted in increased tolerance of the dog to the contrast substance.

Most of the deaths following angiocardiography in patients occurred in those with congenital heart disease and cyanosis, usually after a repeat injection.[1-3] The fatality has been related to the left-to-right shunt which causes venous blood and contrast medium to enter the systemic vessels and precipitate a fatal medullary depression and/or cardiac arrhythmia. It is indeed difficult to evaluate the least toxic or the most dangerous dye on the basis of the fatalities reported, because of the differences in circumstances and conditions under which the contrast media were used. If the cardiac responses in experimental animals were the same as in man, these studies would suggest that a cardiac risk attends coronary arteriography and angiocardiography involving procedures in which the contrast medium reaches the coronary circulation in high concentrations, as in left ventriculography and aortography. It would also appear that Urokon and Hypaque should be used with caution because of their relatively marked

cardiotoxic effect. Diodrast, inspite of its salutary effects on the heart, has been shown to produce serious complications and death[1,3] following its intravenous administration, such reactions probably being noncardiac in origin, whereas Renografin has been used extensively in pyelography and cerebral angiography without any accompanying serious complications.[12,13] Our studies show that Renografin and Cardiografin have relatively fewer cardiotoxic effects and therefore deserve further clinical trial as contrast media for angiocardiography.

SUMMARY

The cardiac effects of intracoronary arterial injections of various contrast substances on coronary blood flow, myocardial contraction, and the electrocardiogram were studied. Urokon, Hypaque, Cardiografin, Renografin, and Diodrast (in the descending order of effectiveness) produced cardiac arrhythmias and ST-T wave changes in the electrocardiogram, depressed the contractile force of the heart, and caused a drop in blood pressure. All of the radiopaque dyes increased coronary blood flow following intracoronary injections.

The authors wish to express their appreciation to Mr. Herbert M. Neiman, Clinical Research Associate, E. R. Squibb & Sons, for supplying the Renografin and Cardiografin.

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Case Reports

Functional Distention of the Kidney in Perinephritic Hypertension

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In a recent report, we concluded: "In its functional state, the kidney appears to be only one-third parenchymatous cells; these surround, and are surrounded by, large volumes of fluid. Summating the volumes of tubular lumina, vascular blood, and interstitial fluid, fluids in transit for processing by the organ apparently comprise some two-thirds of its functional volume."[1] Evidence to support this hypothesis is derived from three sources: first, morphologic study of kidneys which were instantaneously frozen in situ and while functioning, in very cold isopentane, in order to preserve unchanged their functional architecture[1]; second, examination of the fluids which naturally drain from the organ when the inflating force of the blood pressure is removed[2,3]; and third, study of the behavior of radioactive albumin and red cells as they traverse the functioning kidney.[4] The volumes of fluid involved, in per cent of the functional organ, are apparently these: tubular urine, 24; vascular blood, 16; and interstitial fluid, 28. The function of the distention with blood and interstitial fluid is apparently to furnish a special circulation of plasma to the tubular portions of the nephron; the peritubular capillaries are thought to be very porous: they "seine out" the red cells, allowing a profuse flow of plasma to distend the interstitial compartment and to come into utmost intimacy with the tubular cells.[2,3] In part, then, there is essentially an "open circulation" for plasma in the organ, to be compared with the open circulations of invertebrates. The presence of the functional distention is dependent upon the blood pressure[5,6]; the kidney is inflated by the blood pressure, just as a balloon is inflated by the pressure of a forced expiration.

In the present study, the effect of experimental perinephritis on this natural distention was examined. The type of perinephritis used was that of Soskin

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This work was supported by a grant from the Life Insurance Medical Research Fund.
Received for publication June 24, 1959.

and Saphir.[7] It produces not only an azotemia, as they reported originally, but also malignant hypertension and a fatal uremia exactly similar to the syndrome reported by Goldblatt to follow severe renal arterial constriction in the dog.[8] The effect on the renal distention (with blood and interstitial fluid) and also on blood pressure and intrarenal pressure will be described. In subsequent papers, the course of the fatal uremia, analysis of the electrolyte composition of the distending fluids, and measurements of tubular function will be presented.

METHODS

Perinephritis was produced in dogs by incarcerating one kidney in a stiff collodion hull[7] and removing the other kidney. The anesthetic used was morphine sulfate, 2 mg./Kg., followed in an hour with sodium pentobarbital to effect. After one kidney had been exteriorized, it was wrapped with collodion-soaked bandages; about six of them, each one ten inches long, were used. They were wrapped snugly, covering the kidney completely except for a 1-cm. hole at the hilus for entry of artery, vein, and ureter. "Collodion, USP" was used; "Collodion Flexible, USP" is not satisfactory. After allowing the collodion to harden, the kidney was returned to the peritoneal cavity. Then the contralateral kidney was removed and weighed.

Blood pressures were measured in the unanesthetized animals by femoral arterial puncture; recording was optical, using a glass Bourdon tube as the transducer. Intrarenal pressures were measured by the method of Swann, Montgomery, Davis and Mickle.[9] In the dogs on which this measurement was made the incarcerated kidney had been explanted to a subcutaneous position, thus permitting the needle used in the measurement to be inserted directly into the renal parenchyma after it had been passed through the skin and the collodion hull.[10,11] No anesthesia was employed. It is thought that with this technique the pressure in the interlobular veins is measured.[12] This pressure is presumed to be close to that of the inflated peritubular vascular bed and the associated interstitial space.

For necropsy, the dogs were anesthetized with sodium pentobarbital. The incarcerated kidney was dissected free from adherent tissue, along with its artery, vein, and ureter. The latter was cannulated with a 20-cm. length of plastic tubing. Urine was collected and the blood pressure measured. Then, while the organ was still functioning, the renal artery and vein were clamped, and the organ removed, placed in a beaker and allowed to drain. Contamination of the draining fluids with urine was prevented by keeping the tip of the ureteral cannula outside of the beaker. Usually, no fluid drained spontaneously from the incarcerated kidneys, in contrast with the gush of fluid which occurs in normal kidneys. In explanation, the surface of the kidneys adheres strongly to the inner surface of the hull and thus shrinkage and drainage are prevented. When gently dissected free from the collodion hull, fluid flows out freely. Heparin was used as anticoagulant; after 15 minutes, the drained fluid was collected and its volume and hematocrit measured. The drained organ was weighed, and a sample of the dog's arterial blood obtained for measurement of its hematocrit. Unilaterally nephrectomized dogs served as controls: the fluids distending their kidneys were measured in the same way at 4 to 8 days following operation.

The following were calculated: (A) *Relative increase in weight of the perinephritic kidney, the collodion hull having been removed:* The ratio of perinephritic weight less preoperative weight to preoperative weight, expressed as per cent, furnished these data. For "preoperative weight," the kidney was assumed to weigh the same as its contralateral partner, this having been weighed after its removal at operation. Because the two kidneys of dogs weigh much the same, the correlation coefficient between the two weights being 0.98,[13] this method furnishes a good measure of the compensatory hypertrophy that occurred in the incarcerated kidneys. It is the method used by MacKay, Addis, and MacKay.[14] (B) *Functional distention of the organs:* The ratio

$$\frac{D \times 100}{D + W}$$

when D represents the volume of fluid draining, and W the weight of the drained organ, gives this measurement. It is, densities being neglected, the milliliters of fluid draining per 100 grams

of functionally distended kidney. (C) *The factor F, this representing the fraction of the kidney's distending fluids which is interstitial fluid*[2,15]: It is given by the ratio

$$\frac{B - K}{B}$$

when B represents the hematocrit of systemic blood and K represents that of the kidney's distending fluids. By definition, F refers to a fluid which is free of red cells. (D) *The volume of interstitial fluid in the distending fluid:* When F is multiplied by the functional distention (see B above), this gives the desired figure. It is expressed in milliliters per 100 grams of naturally distended kidney. (E) *The volume of vascular blood in the kidneys:* Subtraction of the volume of interstitial fluid (D) from the total distention (B) gives this quantity, again expressed in milliliters per 100 grams of distended kidney.

RESULTS

1. *General Observations.*—The perinephritic dogs experienced malignant hypertension (see below) and fatal uremia. Anorexia was usually complete. Polyuria, hyposthenuria, and isosthenuria occurred in most. Severe vomiting and diarrhea, coma and depression, occasional convulsions, edema, anemia, and severe ocular pathology were present. In addition, chemical changes characteristic of uremia were observed: a pronounced azotemia (plasma ureas up to 500 mg. per cent), anemia, hyponatremia, and low plasma protein content. At autopsy, gross bleeding—a necrotizing arteriolitis—occurred in many viscera. Careful gross and microscopic examination of the kidneys, however, revealed minor or no pathologic change in this organ. In spite of the fact that the animals died in uremia and renal failure, none of the customary renal changes of the disease were evident. The same was reported by Goldblatt[8] for dogs with severe renal arterial clamping.

In a few dogs, however, uremic symptoms did not appear: of 71 dogs operated upon, 7, or 10 per cent, may be called "atypical"; i.e., before autopsy they had not shown signs of diarrhea or ocular pathology or isosthenuria or anorexia. It is our impression that about 3 per cent will survive the operation. But in the great majority, death occurred, on an average, about six days postoperatively. Of the half that survived beyond this, profound depression and a devastating cachexia occurred, with 90 per cent of the animals dead by the fifteenth day. In the present study, the animals were brought to necropsy on a given day regardless of their condition. About 30 experimental animals furnish the data, in 21 of which renal distention was measured.

2. *Blood Pressures and Arrhythmias.*—Fig. 1 shows the mean blood pressures observed following operation, these being calculated from the measured systolic and diastolic pressures by adding to the diastolic pressure one third of the pulse pressure. A group of 12 dogs furnished these data; for a given day, measurements of the blood pressure in 3 to 5 dogs in the group gave the points. In 4 of the 12 animals, observations were taken every one or two days until death. The figure shows that the mean blood pressure usually started to rise even on the first day postoperatively. By the second day it reached, on the average, about 170 mm. Hg and stayed at this level until death. Severe ocular pathology was frequent in the dogs, with massive fibrinous exudates in the anterior chamber and retinal detachment. At autopsy, widespread necrotizing

arteriolitis, even in dogs dying as soon as four days postoperatively, was found, involving the stomach, small intestine, colon, pancreas, myocardium, diaphragm, and brain. All of these assorted observations testify to the fulminating and malignant character of the hypertension.

Individual serial records of systolic and diastolic pressures of 2 dogs out of the group of 12 are shown in the same figure. Dog A died on the fourth day postoperatively and Dog B, on the ninth. The rapid rise in blood pressure is evident. On the second postoperative day, Dog A's pressure was 280/147 mm. Hg, the highest blood pressure observed in the series.

Arrhythmias and bradycardia were observed in all dogs at two to four days after operation. Heart rates decreased from the normal of about 100 to 60 to 90 at this time. Then, from five to eight days postoperatively, although blood pressures remained high, both arrhythmias and bradycardia disappeared.

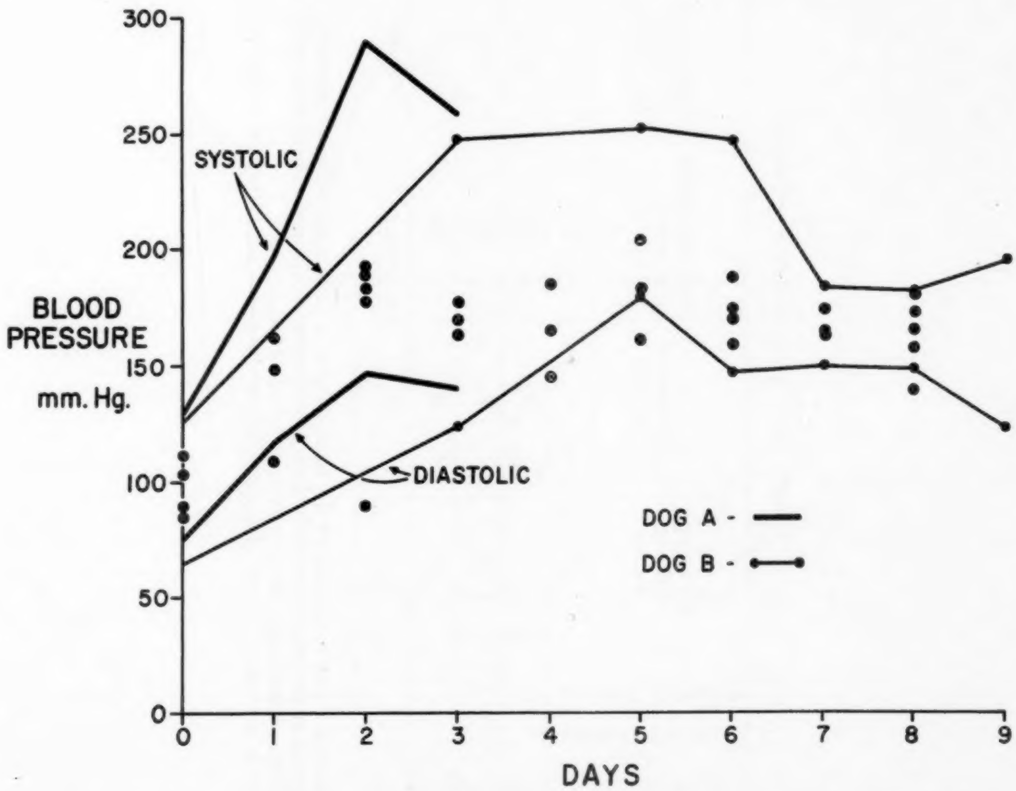

Fig. 1.—Blood pressure in dogs following operation. The encircled points are the observed mean blood pressures of individual dogs, many of which were taken serially. Individual systolic and diastolic pressures are shown for two dogs, *Dog A* and *Dog B*.

3. *Intrarenal Pressure.*—Fig. 2 shows the intrarenal pressures in a group of 14 dogs, in some of which several readings were taken. Most were taken from unanesthetized dogs, but 6 of the readings were taken with the animal anesthetized. This pressure averages 26 mm. Hg in normal dogs,[16] but as the figure shows, during perinephritis it increased very rapidly. On the first day after operation

TABLE I. FUNCTIONAL DISTENTION: AVERAGES*

	MEAN BLOOD PRESSURE (MM. HG)	HYPERTROPHY (PER CENT)	RELATIVE KIDNEY WEIGHT (GM./KG.)	PER CENT OF DISTENTION (ML./100 GM.)	F	DISTENTION	
						BLOOD, (ML./100 GM.)	INTERSTITIAL FLUID, (ML./100 GM.)
50 Normal Dogs	105†	—	5.8	30.5	.50	15.0	15.5
Unilateral Nephrectomy, 4-8 days	—	20	3.0	28.7	.48	14.7	14.0
Perinephritis, all dogs	166	23	3.4	17.9	.42	10.2	7.2
Perinephritis, severe symptoms	161	29	3.4	15.7	.37	10.0	5.7
Perinephritis, mild symptoms	174	15	3.3	20.9	.50	10.5	10.4

*Subjected to statistical analysis, with correction for the small number of cases involved in the perinephritic sample, the differences between means for the following comparisons is significant at the 99 per cent confidence level: means of the perinephritics compared with the normal group of 50 dogs with respect to blood pressure, total distention, blood distention, and interstitial fluid distention.

†For normal blood pressure in the dog, the figure of Katz, Friedman, Rodbard and Weinstein[17] is used.

it rose to an average of 67, and on the second day to 100 mm. Hg, where it remained. Blood pressures were also taken on many of these animals: in 5 dogs whose mean blood pressure ranged from 175 to 190 mm. Hg, the average intrarenal pressure was found to be 95 mm.

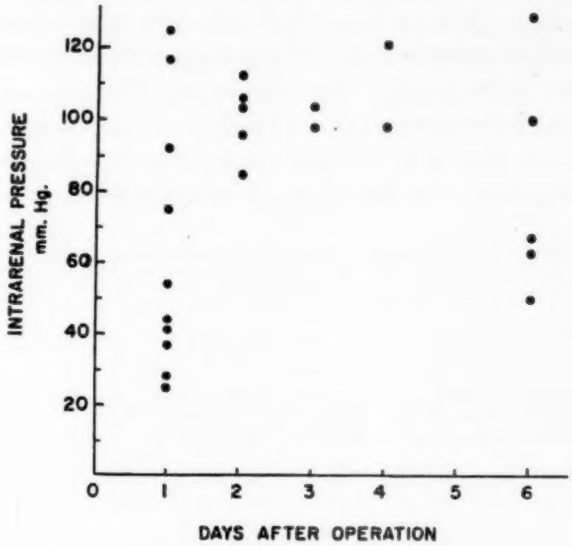

Fig. 2.—Intrarenal pressure in perinephritis.

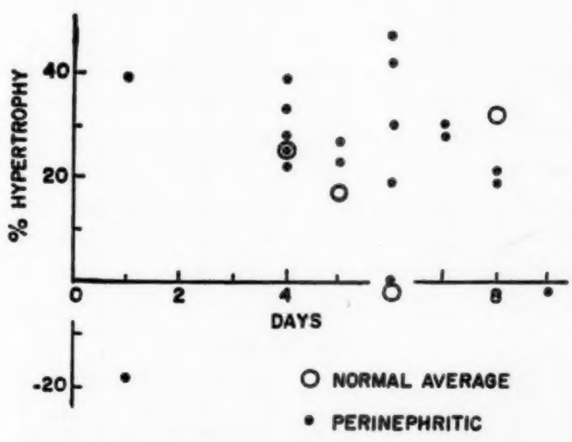

Fig. 3.—Hypertrophy following uninephrectomy.

4. *Compensatory Hypertrophy.*—Fig. 3 shows the increase in kidney weight that occurred both in perinephritic kidneys and in normal kidneys following unilateral nephrectomy. Averages for 2 to 4 animals on each day furnish the data for the uninephrectomized controls. The figure shows that compensatory hypertrophy took place in the incarcerated kidneys as fast as it did in the nonincarcerated kidneys. By the fourth day, all had gained some 30 per cent in weight. Table I shows the average hypertrophy for each group, and Table II shows individual data on the perinephritic dogs.

5. *Distending Fluids.*—Table I shows the characteristics of functional distention in five groups: dogs with normal kidneys (averages for 50 dogs), those following uninephrectomy, 4 to 8 days (averages for 11 dogs), the whole group of those with perinephritis and uninephrectomy (21 dogs), those with perinephritis with severe symptoms, and those with perinephritis with mild symptoms (see below). Uninephrectomy evidently does not influence the relative functional distention of the kidney, in spite of the compensatory hypertrophy shown to occur, for both normal dogs and uninephrectomized dogs had about the same relative functional distention (Table I). The total is about 31 ml. per cent, with 15 per cent due to blood and 16 per cent due to interstitial fluid. In 21 perinephritic animals, considered as a homogeneous group, the total dis-

TABLE II. FUNCTIONAL DISTENTION IN INDIVIDUAL DOGS

DOG NUMBER	DAY OF AUTOPSY	MEAN BLOOD PRESSURE (MM. Hg)	HYPERTROPHY (PER CENT)	RELATIVE KIDNEY WEIGHT (GM./KG.)	PER CENT OF DISTENTION (ML./100 GM.)	F	DISTENTION: BLOOD (ML./100 GM.)	DISTENTION: INTERSTITIAL FLUID (ML./100 GM.)
Severe Symptoms								
1.	4	176	33	3.4	14.2	.42	8.2	6.0
2.	4	—	28	3.7	10.7	.48	5.6	5.1
3.	4	140	25	2.4	15.4	.04	14.8	.6
4.	4	—	23	3.3	7.3	.46	3.9	3.4
5.	4	143	39	2.6	17.6	.28	12.7	4.9
6.	5	211	23	3.4	24.0	.44	13.4	10.6
7.	5	161	27	2.8	24.1	.51	11.8	12.3
8.	6	147	47	5.6	13.1	.39	8.0	5.1
9.	6	127	30	4.6	11.7	.28	8.4	3.3
10.	6	140	0	2.9	15.0	.37	9.4	5.6
11.	6	193	42	3.4	11.7	.47	6.2	5.5
12.	7	170	30	3.0	22.9	.26	16.9	6.0
Averages*		161	29	3.4	15.7	.37	10.0	5.7
Mild Symptoms								
13.	1	139	39	2.9	18.6	.44	10.4	8.2
14.	1	160	−18	3.4	22.2	.43	12.7	9.5
15.	6	—	19	2.9	19.2	.52	9.2	10.0
16.	7	—	29	3.5	10.8	.57	4.6	6.2
17.	8	180	19	3.2	19.5	.54	9.0	10.5
18.	8	157	20	2.9	23.3	.49	11.9	11.4
19.	9	—	− 2	3.2	28.4	.65	9.9	18.5
20.	22	194	23	3.2	23.8	.38	14.8	9.0
21.	57	214	9	4.3	22.6	.48	11.8	10.8
Averages*		174	15	3.3	20.9	.50	10.5	10.4

*Statistical analysis of the difference in means for the two groups shows the following to be statistically significant at the 99 per cent confidence level: total distention and interstitial fluid distention. The difference in means for compensatory hypertrophy and for F are significant at the 95 per cent confidence level.

tention is much less, averaging 18 per cent, with 9 per cent being vascular blood and 8 per cent being interstitial fluid. All of this group had high blood pressures. (Uninephrectomy does not cause an increase in blood pressure.[18])

Table II presents individual data for all the perinephritic dogs; they are divided into two groups, those with severe symptoms and those with mild symptoms. The latter showed either normal appetite or urine specific gravities greater than 1.020, or both. For example, Dog 16 had no loss in weight but was hyposthenuric. Probably it would have survived indefinitely. Dogs 20 and 21 ate well, and definitely would have survived. Dogs 13 and 14, sacrificed one day following operation, were classified as "mild" in the sense that their urines were normosthenuric. But in all of this group in which blood pressures were measured, hypertension was observed.

Table II shows considerable variation in the perinephritic animals. What all have in common is a reduction in total distention of their kidneys. Hence, we ascribe the hypertension to this change, as will be discussed below. If one attempts to ascribe the hypertension to primary reduction in, say, the blood distention, the attempt fails because several dogs (Dogs 5, 6, 7, 12, 14, 20, and 21) had good blood distention. Similarly, Dogs 7, 18, and 19 had good interstitial distention, but still were hypertensive. Apparently, the total distention is the critical change.

Table II shows certain differences between those with mild symptoms and those with severe. (Those with "mild symptoms" were not anorexic and/or hyposthenuric.) Both groups had the same kidney weights, expressed as grams per kilogram of body weight, and both had the same blood distention. But in a comparison of those with mild symptoms and those with severe symptoms, the former had statistically less hypertrophy, greater total distention, greater fractions of interstitial fluid (the normal quantity, in fact, since F equaled 0.50), and much greater volumes of interstitial fluid. As will be discussed below, the critical change in the dogs with induced hypertension is thought to be the reduction in total distention, whereas the added change that produced a uremia so severe as to be fatal was that of very severe reduction in distention of the interstitial fluid space.

DISCUSSION

The sequence of events following the operation is apparently this: The collodion hull shrinks somewhat, compressing the kidney; but more important, the unilateral nephrectomy stimulates compensatory hypertrophy in the remaining kidney. This occurs as rapidly in the incarcerated kidneys as it does in normal kidneys. However, there is not room enough in the stiff hull for both the newly growing tissue and, as well, the fluids which naturally distend the kidney. The new tissue then pre-empts any available space—it grows into the space normally occupied by renal vascular blood and interstitial fluid. The natural distention of the kidney is then reduced to 17.9 ml. per cent from its normal of 28.7 ml. (Table I). This amounts to a reduction to 62 per cent of the normal distention. The blood compartment and the interstitial compartment

share about equally in the reduction, i.e., to 63 per cent and 58 per cent of their normal volumes (Table I). It is the reduction in total distention which we postulate to be the critical change that stimulates the hypertensive response; as indicated above, the stimulus is apparently not reduction, taking them singly, in either the blood compartment or the interstitial compartment. It must also be designated as a relative reduction, since neither unilateral nephrectomy or even three-quarters nephrectomy,[18,19] in both of which the animals' total volume of distention is much reduced, are adequate stimuli for the response. It is the reduction in distention relative to the amount of functional tissue which is evidently responsible.

The reduction in distention is thought to cause secretion of renin, with subsequent formation of angiotensin. This is the kidney's own feed-back mechanism to protect its peculiar circulatory apparatus: it ensures to the kidney its own proper blood flow and pressure, with consequent formation of the special inflated interstitial compartment. The very high intrarenal pressures which were observed reflect the action of the feed-back mechanism and the consequent high blood pressure; because of the constricting hull, however, restoration of vascular volume and interstitial volume to normal was impossible. The intrarenal pressures (probably interlobular venous and interstitial pressures[12]) are considerably higher in this experiment than they were found to be in the perinephritis produced by irritative cellophane[10]: about 100 mm. Hg as compared with 60 mm. Hg. Reflecting this difference is the less malignant course of the disease in irritative perinephritis. In the one a gradual thickening of the capsule slowly reduces the natural distention,[20] whereas in the other a rapid compensatory hypertrophy into a restricted space reduces the distention explosively over a few days.

The fundamental hemodynamic change in the kidney which invokes hypertension has long been a puzzle. Commonly, it is ascribed to renal ischemia, but firm proof that this is indeed the cause has not been forthcoming. In many experimental renal hypertensions the renal blood flow is not reduced,[18,21,22] and attempts to prove that anoxia or hypercapnia,[23,24] resulting perhaps from the ischemia, are the fundamental change have not been successful. We postulate that reduction in the kidney's natural distention is this fundamental change—it is the critical "perturbation of vascular function" in the kidney, as Smith[25] has called it. Braun-Menendez[18] writes: ". . . it is possible that the diminution of pressure in the capillaries which irrigate the tubular cells alters their function or permeability in some fashion." This alteration, we postulate, is not a reduction in pressure, but rather a reduction in the natural distention of the peritubular region.

In the present experiment, encroachment by compensatory hypertrophy on the naturally distended spaces is thought to have caused the hypertension. Tying constricting ligatures around the kidney similarly reduces the distention and produces the hypertensive response.[26] The same is brought on by defects in capsular growth[27] or abnormal growth of a constricting capsule in irritative perinephritis.[20]

In the case of renal arterial constriction the initial event is somewhat different, but it leads to the same fundamental change and the same response: the low blood pressure distal to a renal arterial clamp[19] is presumably insufficient to inflate the kidney with blood and interstitial fluid, for the inflation depends upon the blood pressure to the kidney.[6] This is accompanied by a decrease in intrarenal pressure.[10] If arterial constriction is extreme, it leads to malignant hypertension and uremia, just as in the present experiment.[8] To the reduction in distention the kidney responds with the only feed-back mechanism available to it: elaboration of renin (and the other reactions whose nature is still obscure[28]) that produces high blood pressure and restoration of the kidney's natural distention. In the experiments of Mason, Robinson and Blalock,[19] blood pressures distal to the constricting Goldblatt clamps were often restored, as hypertension developed, to the level observed for systemic blood pressure before renal arterial clamping. Evidently, renal distention is "set," by means of the feed-back mechanism, at a quite constant level. The system apparently responds rapidly, for the sudden onset of shock invokes it.[29] Ogden[29] postulates that it is one of the natural homeostatic reactions for blood pressure in the whole body, but in our view its operation is devoted to maintaining renal homeostasis only. Sometimes indeed, as in malignant renal hypertension, it appears to be disastrously self-centered.

The theory puts the onus of etiology in renal hypertension, not on renal blood flow or blood pressure, but rather on the kidney's natural distention. The two are of course closely related, for reduction in the former, along with reduction in the peritubular vascular pressure, would usually be followed by reduction in the latter. In theory, the two might be differentiated: there might be a normal blood distention and perhaps flow, but a reduction in the total distention, and hence hypertension. Seven dogs in the present series fit into such a category: Dogs 5, 6, 7, 12, 14, 20, and 21 all had a distention of their blood compartments with 12 or more ml. per cent of blood, a region within one standard deviation of the mean of the blood distention in normal animals. But the volume of their interstitial compartments was reduced to about 8.7 ml. per cent; the total distention was thus reduced, bringing on the hypertensive reaction. These cases are uncommon, of course, just as they are in other experimental hypertensions.[18,28]

The hemodynamic defect, then, is thought not to be one of ischemia or metabolism, but a rather simple physical defect in the functional morphology of the peritubular circulatory apparatus: a failure of distention of this region with its special interstitial circulation. If this could be reinflated, then the hypertension should be abolished. This is what was done by Weeks, Steiner, Mansfield and Victor[30]: they revascularized the peritubular, but not the glomerular, vascular beds in Goldblatt hypertensive dogs by means of a splenorenopexy. The animals' blood pressure returned to normal after the operation, just as would be predicted from the present theory. Kohlstaedt and Page[31] theorized that reduction in renal pulse pressures is responsible for the hypertensive reaction. However, these are increased in perinephritic hypertension.[10] Ogden[29] suggested a similar theory which holds that reduction in renal expansile pulses is responsible. This theory is attractive, notably since vascular pulses are known to greatly

promote lymph and interstitial fluid flows.[32] Such a characteristic would be extremely useful in promoting flows of plasma into and out of the renal interstitial compartment, with a "tidal flow of tissue fluid" around the renal cells, in Lamport's picturesque phrase.[33] The balance of evidence, however, is opposed to the hypothesis that renal pulses are in any way important to the kidney's function[34,35] (but see the report of Hawthorne and associates[36]).

The uremic syndrome in 13 of these dogs will be discussed in more detail in another paper. However, the present data explain in part its severity. Two groups of animals were observed, one with mild symptoms (not anorexic and not isosthenuric) and a second with severe symptoms. The cause for the difference apparently resides in the somewhat less compensatory hypertrophy experienced by the former group: 15 per cent as compared with 29 per cent (Table I). In those with mild symptoms, the growing tissue apparently preempted less space than in those with severe symptoms, thus leaving more room for the distending fluids. The blood distention in each group was about the same, viz., 10 per cent. But the interstitial distention in those with severe symptoms was greatly reduced: to 6 per cent as compared with 10 per cent for those with mild symptoms. It is this difference in volume of interstitial fluid which is thought to be fundamentally responsible for the fatal uremia in the group with severe symptoms. This is a functional alteration only: no pathologic change, using conventional histologic techniques, was apparent in these kidneys, just as Goldblatt[8] reported for dogs dying of uremia after severe renal constriction. With proper techniques (i.e., instantaneous fixation[1]), it would presumably have been visualized as a failure of functional distention.

The fatal uremia consequent to this change in functional morphology of the kidney gives a clue to the fundamental import of the kidney's natural distention. We have postulated that the kidney normally has a profuse circulation of plasma into a large extraendothelial space. This brings plasma into utmost intimacy with the surface of all tubular cells (and perhaps even into extracellular canaliculi inside the cells themselves[3]), an intimacy great enough so that the organ can extract from its perfusing blood virtually all of actively excreted substances, such as Diodrast.[2,3] But if, as in the present experiment, this space is reduced, then the cells simply are not presented with enough plasma to work on. In this case the organ loses the flexibility and adaptability which it customarily has: it can't adjust the electrolytes of the blood, it can't adjust the pH, it can't excrete into the urine the substances which are actively excreted, it can't produce a concentrated urine. It is the presence of a large area of tubular parenchyma, to which is exposed an enormous volume of plasma, which confers on the kidney its unique abilities. It is this which was lost in the present experiment: it was a defect in the peritubular circulatory apparatus. It can evidently be a defect in volume flow of whole blood through the peritubular vascular system or a defect in plasma flow through the extraendothelial space, or perhaps both. The peritubular circulatory apparatus, then, is a special adaptation of the renal circulation which results in exposure of a large area of the tubular cells to a large flow of plasma. It is this which gives the kidney its great efficiency in the rectification of the plasma to homeostatic equilibrium. In the present experiment,

in the dogs experiencing only mild symptoms following the incarceration (fourth group of Table I), the total distention, although reduced in quantity, was still at 21 ml. per cent. This was evidently sufficient to be compatible with life, providing that it was maintained well inflated by the high blood pressure. But if this volume fell to 16 per cent, as in the group with all the severe symptoms of uremia, then there was not enough peritubular circulation to permit homeostatic adjustment, and the animals proceeded slowly into fatal uremia. One can imagine also that the tubules were all crowded together, with surfaces jammed against one another, thus excluding all but a small fraction of tubular surface from the circulating plasma.

The theory may readily be applied to human disease: in acute glomerulonephritis, the cause of the hypertension is thought to be identical with that in experimental Goldblatt hypertension, except that the constricting clamps are put on the glomerular capillaries by the inflammatory process. The same applies in the hypertensions of the Kimmelstiel-Wilson syndrome and eclampsia.[22] In malignant nephrosclerosis the constrictions are in the arterioles. But in all of these the fundamental defect that induces hypertension is thought to reside not in arterioles or glomeruli, but in the vascular bed distal to them, where a low blood pressure consequent to the increased resistance upstream fails to inflate the peritubular vascular and interstitial compartments. In other renal diseases the primary lesion is postulated to be in the peritubular region and not the glomeruli. As the reactions to inflammation of cicatrization and contraction occur, as, for example, in chronic pyelonephritis, the distensibility of the peritubular compartment is reduced and the hypertensive response follows. The main defect in the "scarred contracted kidney" is thought to lie in the peritubular circulation, in both its vascular and extraendothelial channels.

Essential hypertension, it is postulated, is the same with respect to the etiology of the elevated blood pressure: the fundamental change is constraint of the peritubular circulatory apparatus. The disease apparently progresses faster in the peritubular apparatus than in the glomerular apparatus, for filtration rates remain less depressed than does blood flow during the course of the disease. From the observation that blood flow is depressed more than secretory maxima, it is generally concluded that there is ischemia of the tubules.[22] To this may be added the further interpretation that early in the disease the functional defect probably resides in the peritubular vascular compartment and not in the extraendothelial compartment. This is in agreement with the observation that renal hyperemia may occur in pyrexia during the disease: evidently, the peritubular vascular compartment, although constrained, is still labile, just as it is in normal life But the secretory capacity is unchanged in pyrexia, since excretion maxima usually change but little during fever.[22] In interpretation, the interstitial compartment is fixed in the disease and not labile as is the peritubular vascular compartment. Early in the disease, the pathologic lesion is postulated to be functional only, just as in the present experiment, and not detectable by conventional histologic techniques[37]; it is perhaps just a loss of natural elasticity and, therefore, in distensibility (see below). But late in the disease a peritubular vascular and interstitial nephritis occurs.[28] This puts an internal constraint upon the

organ: it is laced through and through with the fibrotic processes, just as in pressure hoses a wire helix is run through flexible rubber tubes in order to stiffen them against inflation pressures. But in the kidney, adequate inflation is necessary for normal function.

Finally, the natural elasticity of the kidney is presumed to be subject to the same aging process as are other elastic tissues, e.g., that in the arteries or the lens of the eye, or the skin.[39] As the kidney stiffens with age, it can be distended to its natural volume only by the expenditure of more energy. The source of energy is the blood pressure, and so, with aging it rises. The high blood pressure of old age, then, it is postulated, is due fundamentally to the natural loss of the kidney's elasticity with aging. In a few, the process runs so slowly that their blood pressure remains essentially at the level of that of 20-year olds. In most, the process runs a little faster; they experience the mild elevations in blood pressure so characteristic of aging. A genetic factor apparently influences this[28]; the process may be as inexorable as loss of elasticity in the lens of the eye, with consequent presbyopia.[40] In still others, the process runs rapidly relatively early in life; they experience the symptom complex designated as "essential hypertension." In all, the onset of inflammatory disease, of whatever kind, greatly aggravates this natural aging process. It is apparent that in this hypothesis we have placed major emphasis on the kidney's elasticity and on its natural distention. But measurements of these two parameters in human hypertension are completely lacking at present and until such measurements can be obtained, the hypothesis must remain in the field of speculation only.

SUMMARY

One kidney of dogs was wrapped in collodion-soaked bandages and the other removed. This caused malignant hypertension, and usually, fatal uremia in about seven days. The fluids draining from the incarcerated kidneys, after the artery and vein had been simultaneously clamped, were analyzed for volumes and hematocrits a few days postoperatively. The volume draining was reduced to 18 ml. per 100 Gm. of functionally distended kidney, as compared with 31 ml. per cent for normal dogs or for dogs after uninephrectomy. Both vascular blood and interstitial fluid were involved in this reduction. A reduction to 21 ml. per cent was found compatible with life. But a reduction to 16 ml. per cent was incompatible with life, for the animals soon died in fatal uremia. Severe reduction in the volume of interstitial fluid was apparently the critical change in the latter case. It is the reduction in functional distention, it is postulated, which is the stimulus to the kidney's own feed-back mechanism of renin secretion; this usually restores functional distention to normal by inflating the kidney with a higher blood pressure. But in the present experiment, this was impossible because of the straight-jacketing effect of the incarcerating collodion hull. The failure of distention then led to malignant hypertension, and finally, when hypertension was extreme, to the inflexible behavior of the kidney which is characteristic of fatal uremia.

At autopsy, the animals were found to have the massive necrotizing arteriolitis characteristic of death with malignant hypertension. However, in the

kidneys there was no histopathologic change. Evidently, the renal morphologic change responsible for the hypertension, and also for the uremia, was a functional change only: it could not be visualized by conventional histopathologic techniques.

The theory is proposed that the critical hemodynamic defect in the kidney that leads to renal hypertension is reduction in the kidney's natural distention. This may happen in a variety of ways: by an incarcerating hull, as in the present experiment; or by partial arterial constriction, with consequent reduction in the inflating action of the blood pressure; or by the constraining effect of cicatrization and contraction in renal inflammation; or by decline in the kidney's natural elasticity with age. All lead to the same response of formation of angiotensin (and other still obscure reactions) which induces hypertension.

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Myxoma of the Left Atrium Simulating Restenosis of the Mitral Valve

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Myxoma is the commonest kind of benign tumor of the heart, and constitutes 50 per cent of the primary cardiac neoplasms. It occurs exclusively in the atria, and in 75 per cent of the instances the left atrium is the site.[1] The infrequency of this tumor is reflected in the medical literature which records 150 cases up to 1952.[2] Since then about 10 cases have been added to the literature in this country.

The clinical picture produced by this tumor in the left atrium is indistinguishable from that of mitral stenosis. The pedunculated tumor, which in most instances fills the whole left atrial cavity, produces some degree of dependent obstruction of the mitral orifice. This causes the functional stenosis of the mitral valve.[3,4] The hemodynamic changes produced by such an obstruction to flow through the mitral valve resemble precisely those of mitral stenosis.[5,11,12] These consist of elevation of the pulmonary arterial and capillary pressures.

In reviewing the literature one is impressed with the fact that this condition is difficult to diagnose during life. In the majority of the cases the tumor is discovered at postmortem examination or during surgical exploration of the heart for supposed mitral stenosis. With recent advances in the cardiac surgical technique, complete removal of the tumor is possible without much hazard, so that the diagnosis of this condition during life is of more than academic interest.

Aside from the fact that in the case to be presented in this paper the intra-atrial tumor was removed completely and successfully by using an open-heart technique, there are other interesting features. The patient had undergone a mitral commissurotomy for rheumatic mitral stenosis 4 years prior to the present admission. Following a brief period of symptomatic relief, her symptoms had recurred and progressed. Physiologic studies obtained by combined heart

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Received for publication April 3, 1959.

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catheterization 4 years after surgery showed evidence of obstruction of the mitral valve. This led to the erroneous diagnosis of restenosis of the mitral valve.

CASE REPORT

G. S., a 47-year-old white woman, was admitted to the Hahnemann Hospital on Sept. 17, 1958, with complaints of easy fatigability, exertional dyspnea, and intermittent palpitations. Recently, she had developed swelling of the ankles, which responded to mercurial diuretics and digitalis therapy. The patient offered a past history of joint pains at the age of 17, suggestive of rheumatic fever.

The patient had been hospitalized three times previously in another institution. She was admitted for the first time in 1953, for abdominal surgery for chronic intestinal obstruction. Following surgery she developed acute pulmonary edema, which responded to the usual therapy. One year later, in October, 1954, she was admitted to the same hospital for evaluation of her cardiac status. The patient then complained of the same symptoms as at the present time. The abnormal physical findings were limited to the heart. A normal sinus rhythm was present. The point of maximal impulse was in the fifth left intercostal space 2 cm. outside the mid-clavicular line. The first heart sound at the apex was sharp, and there was a questionable presystolic murmur. The pulmonic second sound was accentuated. The blood count and urinalysis were normal. The antistreptolysin titer was less than 100 units. The electrocardiogram showed a normal sinus rhythm, with a P-R interval of 0.2 second, and the QRS complexes were within normal limits. A teleroentgenogram showed no cardiac enlargement. There was retrodisplacement of the barium-filled esophagus in the right anterior oblique position, suggesting left atrial enlargement.

A diagnosis of rheumatic heart disease with mitral stenosis was made, and the patient was readmitted to hospital on Dec. 29, 1954, for a mitral commissurotomy. At the time of surgery a dilated left atrium was noticed. The mitral orifice was estimated to be 1.5 to 2 cm.^{2} There was no calcium deposit on the valve leaflets. After "finger fracture" of the mitral valve the mitral orifice was increased to 3 cm.^{2}. It was stated on the biopsy report that the left atrial appendage was normal atrial muscle. The postoperative course of the patient was uneventful except for the development of chest pain, which was considered to be the part of the postcommissurotomy syndrome. This responded to cortisone therapy.

Following surgery there was a brief period during which the patient was improved. However, the symptoms of shortness of breath and fatigability recurred and progressed. She was referred to the Bailey Clinic for re-evaluation. The physical examination at this time showed the presence of a Grade 1, mid-late, diastolic, rumbling murmur, with presystolic accentuation at the mitral area. The teleroentgenogram (Fig. 1) showed cardiac enlargement of moderate size, and there was retrodisplacement of the barium-filled esophagus in the right anterior oblique position. This suggested enlargement of the left atrium, and there was evidence of some enlargement of the right ventricle. The electrocardiogram (Fig. 2) showed deformed P waves, indicating atrial dysfunction.

TABLE I. PRESSURES (IN MM. HG) AT CATHETERIZATION

Right atrium	(3)
Right ventricle	26/4
Pulmonary artery	28/18 (13)
Left atrium	(12)
Left ventricle	82/3
Brachial artery	90/55
Left atrium-Left ventricular gradient	8

Figures in parentheses denote mean pressure.
The cardiac output was not measured since the procedure had to be terminated because of intense bradycardia.

The P-R interval was 0.18 second, and nonspecific T-wave changes, probably due to digitalis, were noted. A combined heart catheterization was performed in order to evaluate the hemodynamics (Table I). The left atrial pressure was elevated, and a definite atrioventricular gradient was present (Fig. 3).

Fig. 1.—Teleroentgenogram of the heart in posteroanterior and right anterior oblique positions. For explanation see the text.

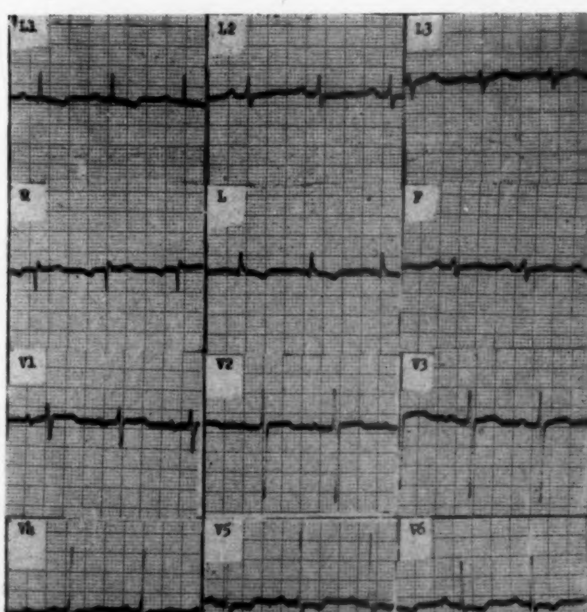

Fig. 2.—Twelve-lead electrocardiogram of the patient. For explanation see the text.

The clinical picture and the physiologic studies were consistent with restenosis of the mitral valve,[13] and the patient was regarded as a suitable candidate for mitral commissurotomy. She was operated upon on Sept. 22, 1958, by one of us (H.T.N.). The left atrium was approached through a right thoracotomy incision,[6] and during exploration of the left atrium a huge tumor, occupying most of the left atrial cavity, was palpated by the exploring finger. The mitral valve and the mitral orifice were felt to be normal. Since it was not feasible to remove the tumor by the surgical technique employed at this time because of the extreme friability of the tumor, and because

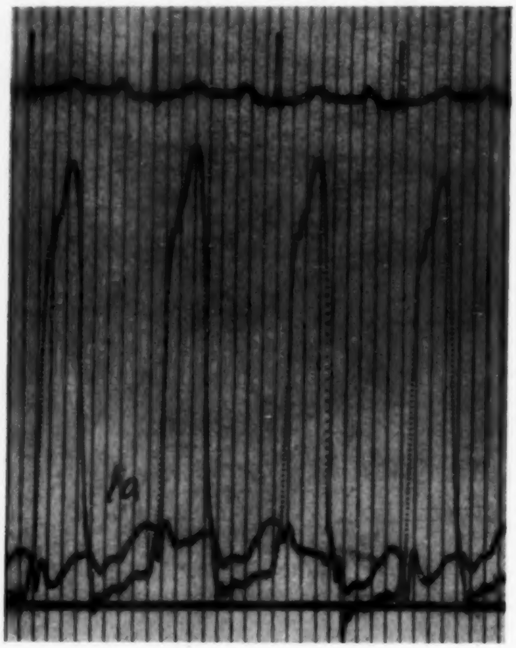

Fig. 3.—Simultaneously recorded left atrial and left ventricular pressure tracings show atrioventricular filling gradient. For explanation see the text.

Fig. 4.—Photograph of the left atrial myxoma attached by a pedicle to the interatrial septum.

of fear of producing systemic emboli, the definitive procedure was postponed until a later date and the chest was closed. The patient was reoperated upon on Oct. 4, 1958, and this time a pump-oxygenator was used to bypass the heart and lungs. When the left atrium was opened, a tumor, 7 by 6 by 3.5 cm. in size, was seen to be attached by a pedicle to the interatrial septum above the origin of the mitral valve leaflet (Fig. 4). The tumor was removed completely. The recovery of the patient was uneventful, and she was discharged from the hospital on Oct. 22, 1958.

The tumor was of firm consistency, and its surface was covered by a grayish membrane which was adherent to the underlying tissue. The numerous sections of this mass when examined under microscope showed that the tumor was composed of acellular material with areas of myxoma-like stroma. There was infiltration by numerous capillaries and fibroblasts. A variable number of erythrocytes and amount of hemosiderin pigment were present (Fig. 5). The patient was seen 6 months after the operation, and was symptom-free. No murmur was heard on auscultation of the heart.

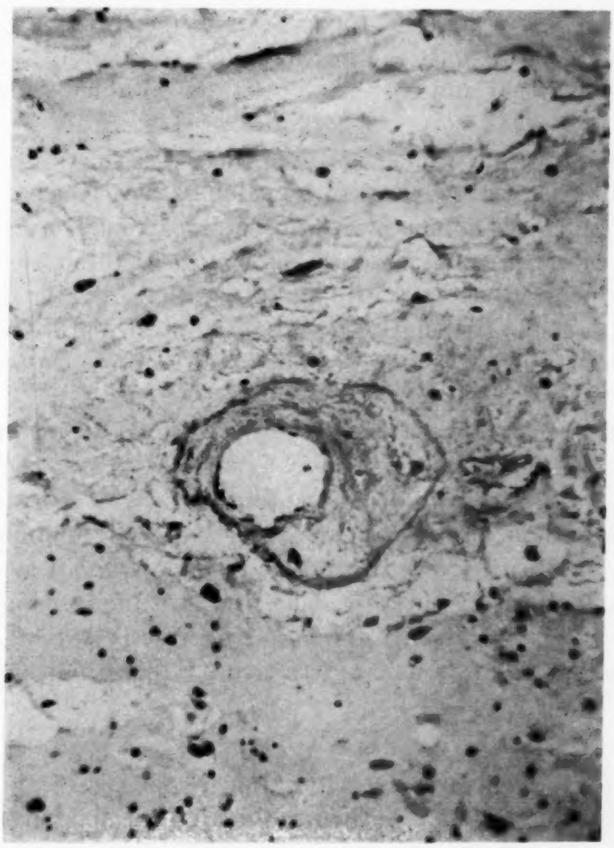

Fig. 5.—Microscopic picture of the section of the tumor. For explanation see the text.

COMMENT

The clinical picture, physical findings, and the laboratory investigations in this case were entirely consistent with refusion of the mitral valve. The futility of examination by electrocardiogram and x-ray in diagnosing myxoma of the left atrium is quite evident here and in agreement with the findings of other workers.[7] The cardiac catheterization showed elevated left atrial pres-

sure with tall "a" waves and the presence of an atrioventricular filling pressure gradient. These findings are quite characteristic of mitral stenosis.[11] The use of angiocardiography as a diagnostic procedure is suggested in suspected cases of this condition.[5] However, the routine use of this test in every case of mitral stenosis for the differential diagnosis is impracticable.

It has been emphasized in the literature that the tumor of the left atrium may be suspected under the following circumstances: (1) When there is absence of a history of rheumatic fever, with auscultatory signs of mitral stenosis. It should be remembered, however, that in 50 per cent of the cases of mitral stenosis a history of rheumatic fever is lacking. (2) When there is a changing character to the murmur with a change in the patient's position. (3) When there is relentless cardiac failure which does not respond to digitalis therapy.[8] (4) When there is a history of syncope related to the posture. The tumor occasionally shifts in such a way that it obstructs the mitral orifice completely. This results in a sudden attack of fainting and a shock-like state. Sudden deaths are reported in some cases.[2]

None of the above-mentioned features was present in our case. The only peculiar feature in this case was the disproportion between the patient's symptoms and the intensity of the diastolic murmur. This particular auscultatory finding is characteristic of early mitral stenosis, and most of the patients presenting it are either free of symptoms or mildly symptomatic. A faint diastolic murmur in severely symptomatic patients presenting a clinical picture of mitral stenosis should make one suspicious of the possibility of the presence of a tumor in the left atrium.

The present case represents the successful removal of an intra-atrial tumor, through the use of a pump-oxygenator to bypass the heart. In the past, a few instances of successful removal of these tumors by the closed-heart technique and under hypothermia have been reported.[9-11] These tumors are extremely friable and their removal under direct vision is necessary if systemic embolization is to be avoided during surgery. The use of a pump-oxygenator is of distinct advantage over hypothermia in an adult or elderly patient, and this should be the method of choice in an attempt to remove this tumor.

SUMMARY

A case of intra-atrial myxoma simulating restenosis of the mitral valve is presented. A past history of mitral commissurotomy and physiologic evidence of obstruction of the mitral valve led to the wrong diagnosis of restenosis of the mitral valve. A pump-oxygenator to bypass the heart during surgery was preferentially used over the closed-heart technique or hypothermia for complete and successful removal of the tumor.

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Isolated Granulomatous Myocarditis

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Chronic myocarditis is a term formerly applied, rather indiscriminately, mainly by morbid anatomists, to any myocardial fibrosis. With increasing recognition of the relation between vascular disease and myocardial scarring, the term is now very rarely used. Some practitioners continue to use the term as a conveniently vague and uninformative label on certificates of illness for employers. Gore and Saphir,[1] in 1947, listed fifty conditions in which the lesions of myocarditis had been found at autopsy. Saphir,[2] in 1953, also recognized isolated myocarditis in which the cardiac lesion predominates clinically and pathologically and is not part of another disease process. This type he further subdivided into (1) diffuse, and (2) granulomatous forms. Granulomatous myocarditis is a rare condition, and close perusal of case reports shows that, in actual fact, pathologically, it is even more uncommon for the lesions to be strictly confined to the heart. The following case is reported of a patient studied in hospital for 12 days before his death, in whom the autopsy lesions were truly restricted to the myocardium.

CASE REPORT

R. B., a 45-year-old English male clerk of works, was admitted to hospital in May, 1952, because of attacks of fainting and unconsciousness, of a few minutes' duration, during the preceding 5 weeks. The first attack occurred during sleep and was accompanied by sweating, dyspnea, emesis, and flatulence. Later the same night there were several fainting attacks of brief duration, with evanescent substernal pain. Almost daily there were subsequent attacks; the patient and his doctor were able to distinguish (1) tachycardia before the attacks, (2) bradycardia, down to 24 per minute during the attacks, and (3) tachycardia, to 122 per minute, recorded after the attacks, with substernal tightness, emesis, and flatulence.

Past and family histories were noncontributory, and the patient had never been abroad. On examination, the ventricular rate was 68 per minute and regular, the blood pressure was 160/110 mm. Hg. The patient looked well, but there was a well-marked apical presystolic triple rhythm and a soft systolic murmur. The patient was blind in the left eye, the retina being degenerate and pigmented, and the lens dislocated on that side. On admission, the electrocardiogram showed right bundle branch block and prolonged atrioventricular conduction time, P-R interval of 0.26 second, QRS duration of 0.15 second, ventricular activation time in Lead V_1 of 0.11 second, and ventricular rate of 63 per minute. On the teleoroentgenogram of the chest the cardiothoracic ratio was 15:30 cm. Hemoglobin was 16.1 Gm. per cent, erythrocyte sedimentation rate 4 mm. in the

Received for publication April 7, 1959.

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first hour (Westegren), total leukocytes 6,800/c.mm., normal differential. The Wassermann reaction and Kahn tests were negative. Temperature throughout his stay in hospital was below the upper normal limit except for one reading of 98.8°F. on the eleventh evening. The patient was kept continuously in bed and treated for atrioventricular block with ephedrin hydrochloride 32 mg. orally thrice daily. On this he complained of brief periods of rapid, regular palpitation, and his blood pressure settled to 130/95 mm. Hg. The triple heart rhythm persisted.

At 9 P.M. on his twelfth day in hospital the patient started to have Stokes-Adams-Morgagni attacks, with loss of consciousness, convulsions, and absent heart sounds for as long as 4 seconds. These attacks became more frequent, and by 10 P.M. he was in almost continuous status Stokes-Adams-Morgagni. The electrocardiograms taken at various intervals during the night showed: (1) complete atrioventricular block, ventricular rate 23 per minute, atrial rate 116 per minute, and left bundle branch ventricular complexes; (2) paroxysmal ventricular tachycardia at 160 per minute, related rather closely to a parenteral injection of epinephrine, and accompanied by a blood pressure of 210/140 mm. Hg and a feeling of extreme pressure in the epigastrium; (3) 2:1 atrioventricular heart block with ventricular rate of 47 per minute, QRS duration of 0.13 second (standard leads only). RS-T segment elevations in Lead I with reciprocal depressions in Lead III suggested necrosis of tissue. Lead III of this record showed a different degree of heart block, with dropped beats and an irregular ventricular beat.

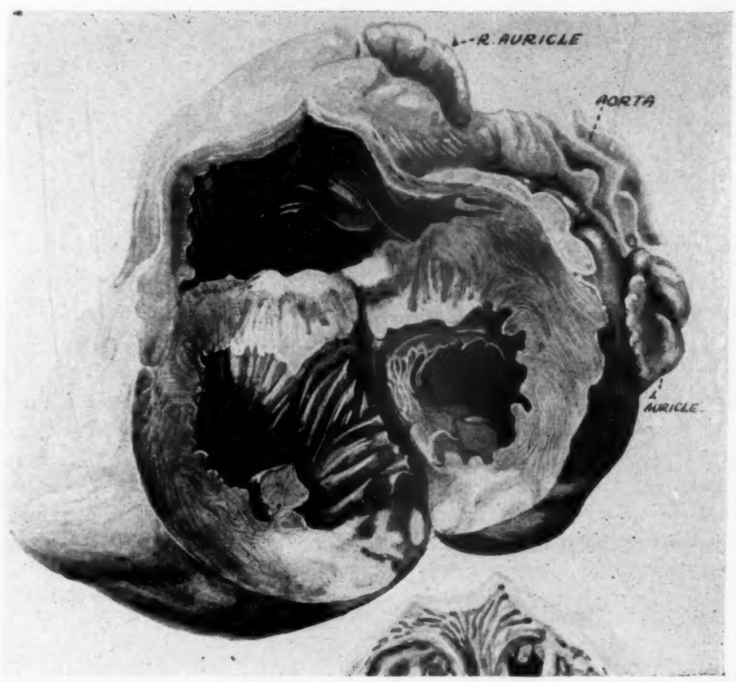

Fig. 1.—Print from artist's impression of heart laid open at autopsy. Involvement of septum and lateral wall of left ventricle is well shown.

For the rest of the night, periods of consciousness lasting from 40 to 60 seconds were associated with a slow, irregular heart beat, and these alternated with periods of unconsciousness lasting for as long as 2 minutes without clinical heart sounds. Therapies included subcutaneous atropine, rapid digitalization with digoxin to combat the signs of heart failure, and terminally once, intracardiac Adrenalin. All of these measures were of no avail, and the patient died at 8:30 A.M. the next morning.

The autopsy took place 3½ hours after death. Apart from acute terminal engorgement of the lungs and abdominal viscera, the abnormalities were confined to the heart. The heart weighed

460 grams, and there was dilatation and hypertrophy of its left side. The tricuspid valve admitted three fingers. Near the apex on the anterior wall there was a subepicardial hemorrhage, the site of the intracardiac injection of epinephrine. There were two right coronary arteries, their orifices being 0.5 cm. apart. The anterior one was small, the posterior larger. The circumflex branch of the left coronary artery was also small, again apparently congenitally. There was some atheroma, especially affecting the anterior descending branch of the left coronary artery, but no important narrowing. The interventricular septum was 17 mm. across, showing in its upper part firm, whitish patches on both sides, with only a small central strip of recognizable myocardium. There were other, smaller, sharply demarcated patches, resembling grayish-white cheese, lower down in the septum, and in the posterior and left lateral walls of the left ventricle (Figs. 1 and 2).

Fig. 2.—Heart autopsy print. The granulomas appear like grayish-white cheese in septum, left above, and lateral wall of left ventricle, right.

Microscopically, there was extensive infiltration, and in many places entire replacement of the myocardium by a diffuse granulomatous process (Fig. 3). Fibrous tissue was plentiful, in particular at the edges, and small round cells, plasma cells, and eosinophils were numerous. Giant cells of the Langhans, foreign body, and myogenic varieties were an arresting histologic feature. Some of these were vacuolated (Fig. 4), and in certain instances, dead sarcoplasm was identified, undergoing phagocytosis in the vacuoles. The microscopic appearances were those of an inflammation, not more than 3 months old, which was becoming chronic, had been acute, and was still active. Special stains revealed no acid-fast bacteria, spirochetes fungi, or other organisms.

DISCUSSION

Diagnosis.—After detection of the lens dislocation, the patient was carefully re-examined, with the syndromes of Weill,[3] Marchesani,[4] and Marfan[5] in mind. There was no suggestion of brachymorphism or dolichomorphism; in fact, skeletally he seemed very normal. At autopsy there was, however, cardiac enlargement, dilatation and hypertrophy of the left side of the heart, not adequately explained by his terminal illness, congenital abnormalities of the coronary arteries, and the pathologist commented on a small thoracic aorta. There is no record of pre-illness blood pressure, and no continued hypertension during the illness; nor did renal histology suggest this. The question arises whether this case should be grouped with the heritable disorders of connective tissue.

McKusick[6] carefully remarks that it is safer to consider all patients with ectopia lentis as being potential victims of the aortic complications of Marfan's syndrome. It is not too difficult to find reports of myocardial lesions in Marfan's disease.[7-9] Mostly fibrosis, diffuse, moderate, and interstitial, is mentioned along with patchy degeneration of muscle cells. In Whitfield's[10] case the fibrosis was predominantly in the septum; there was a left bundle branch type of electrocardiogram, and associated aortic hypoplasia. Death was from heart failure, and the authors use the term "myocarditis," largely, it seems, because of the absence of significant coronary atheroma. If the present case is to be regarded as a forme fruste of Marfan's syndrome, then here is a new and exciting myocardiopathy to be added to an already extensive and protean list of manifestations.

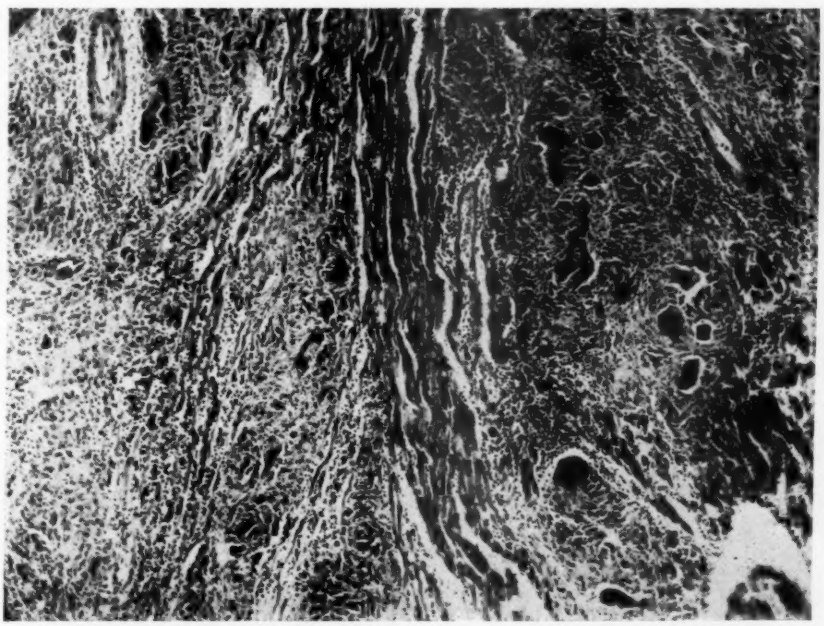

Fig. 3.—Myocardial granulomatous inflammation with necrotic muscle fibers, foreign body (phagocytic) multinucleate giant cells, and infiltration with eosinophils, plasma cells, and small round cells. (Hematoxylin and eosin; magnification, ×55.)

Clinical diagnosis of the terminal illness was extremely difficult. Painless myocardial infarction was considered, but unenthusiastically even when RS-T segment shifts appeared on the electrocardiogram, because of the normal temperature, sedimentation rate, and leukocyte count. Treatment on expiry was still only for "heart block." To suspect the diagnosis in life will require a high index of suspicion on the part of the clinician when faced by an extremely sick patient who has unexplained heart failure or conduction disturbance, or who appears to have had a thoroughly atypical myocardial infarction.

Histologically, the case here described resembles most closely those of Kean and Hoekenga,[11] Tesluk,[12] Magner,[13] and the illustrations in Gould's[14] book,

unaccompanied, unfortunately, by clinical data. Waller's[15] case also showed some histologic similarity, but there were many other features, such as thymoma, menopausal muscular dystrophy, and myositis, also with multinucleate giant cells, of all striated muscle. One regrets that sections of voluntary muscle were not taken in the present case. Apart from this omission, Case No. 2 of Kean[11] and the one here described do seem to be true examples of myocarditis, both giant-cell and granulomatous, in which the lesions were strictly confined to the heart. Tesluk[12] points out that his own case, those of Jonas,[16] Magner,[13] Case 1 of Kean,[11] and the majority of the other cases described were not truly isolated myocarditis, there being additional granulomas, often macroscopic, sometimes microscopic, elsewhere in the body. Favorite extracardiac sites were the lungs, mediastinal nodes, liver, and aortic adventitia.

Primary cardiac amyloidosis, and sarcoidosis of the heart were considered among the histologic differential diagnoses. However, pathologists who saw the sections in London,[17] Leeds,[18] and at the Mayo Clinic[19] were all agreed on the diagnosis of granulomatous giant-cell myocarditis.

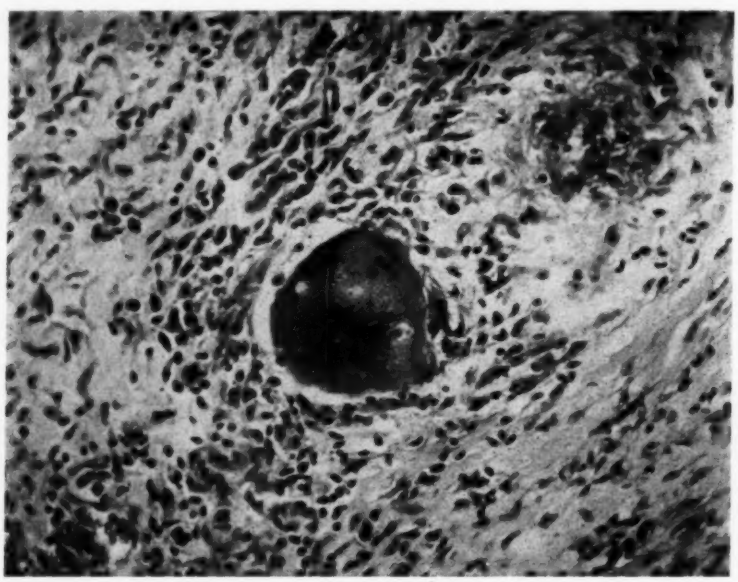

Fig. 4.—Higher power view of myocardium. Degenerate sarcoplasm can be seen in a vacuole in the actively phagocytic multinucleate giant cell in center field. (Hematoxylin and eosin; magnification, ×200.)

Etiology.—On morphologic grounds, the author was inclined to regard the condition as a hypersensitivity inflammation or a deep-seated fungus infection. The restriction of the lesions to the myocardium, and failure to find fungi in sections do not exclude the latter possibility. Paulley and associates,[20] in the United Kingdom, have described myocardial toxoplasmosis without active lesions elsewhere. Among the other cardiopathies considered are coccidioidomycosis, blastomycosis, torulosis, histoplasmosis, and sarcosporidiosis. The author thinks

that in life further diagnostic evidence should have been sought by the prompt application of a battery of skin tests, such as the coccidioidin reaction. Only a very few of these are readily available in this country. The drug Amphotericin B has shown promise in coccidioidomycosis,[21] and despite its toxicity should be started early, particularly if skin tests are positive, while the patient is further studied for mycosis with, for example, dye or complement fixation tests.

A case of eosinophilic and giant-cell granulomatous myocarditis associated with exfoliative dermatitis was attributed by Waugh[22] to penicillin hypersensitivity. Acute interstitial myocarditis[23] has been described in a case of exfoliative dermatitis following the administration of arsphenamine. Šikl[24] asked, in 1936, whether isolated myocarditis might not be classified as idiosyncratic-allergic rather than idiopathic. He described two instances of myocarditis which occurred in syphilitic patients after treatment with Neosalvarsan. Both cases showed an acute eosinophilic myocarditis with granulomatous lesions in which neither mycobacteria nor treponemes could be demonstrated. He believed that some cases of myocarditis might be the result of hypersensitivity, particularly those having a history of urticaria or, as in the cases of Brown[23] and Waugh,[22] exanthematous skin lesions. Franz[25] suggested that the myocardial lesions which he had observed either were the result of the administration of epinephrine or were caused by hypersensitivity to the drug. The present patient certainly received epinephrine, but only for heart block long after the heart disease had manifested itself. Up to his admission to hospital he had received no drugs.

Had the diagnosis been suspected in life, nothing would seem to have been lost by early, cautious steroid therapy. In fact, at the present time most cases of drug allergy with marked skin lesions are treated with cortisone or corticotropin, and it may be that occasionally an unsuspected idiosyncratic myocarditis is simultaneously successfully treated.

SUMMARY AND CONCLUSIONS

1. A case of granulomatous and giant-cell myocarditis is described in which the lesions were restricted to the heart.
2. The difficulty of clinical diagnosis, despite survival with inpatient hospital study for 12 days, is touched upon.
3. Etiologically, syphilis and tuberculosis were excluded.
4. Despite no evident antigen, and failure to find fungi in the stained sections, morphologically, the appearances suggested a hypersensitivity inflammation or a deep-seated fungous infection.
5. A plea is made for the prompt instigation of studies for mycosis if obscure myocarditis is suspected.
6. In view of the extremely bad prognosis of the disease, and usual failure to make the diagnosis ante mortem, treatment cannot wait for diagnostic confirmation. It may need to be started, if the patient is to be treated at all, when the diagnostic formulation is no more than a "clinical hunch."
7. Two thoughts on therapy are put forward based on the suggested etiology.

Thanks are due to Dr. K. D. Keele for permission to publish, and continuous encouragement.

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Variations in the Form of the T Wave in a Case of Partial Heart Block

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Alterations in the form of the T wave with changes in the heart rate were investigated in a series of cases for the first time by Scherf.[1] Changes in the size, shape, or direction of the T wave, as well as changes in the S-T segment in the absence of alterations of the QRS complex were observed following the prolonged pauses of single ventricular and auricular extrasystoles, of blocked auricular extrasystoles, and in partial heart block. In a third of the cases studied, alterations of the T waves in postextrasystolic beats were noted; but among many hundreds of cases of partial heart block, the author found only 2 cases showing the phenomenon. Later investigators dealt with T-wave changes in the postextrasystolic beat only,[2,3] and a search of the available literature revealed no further report of T-wave changes in partial heart block of the type herein described.

Because the occurrence of alteration of the T wave in partial heart block seems so rare, we felt that the report of this case, with its multiplicity of variations in the contour of the T, might be of interest.

CASE REPORT

A 70-year-old Hebrew widow was admitted to the Brooklyn Hebrew Home and Hospital for the Aged for custodial care on March 30, 1957.

Her significant past history was gall-bladder surgery 36 years before, and hypertension of unknown duration.

The blood pressure on admission was 220/90 mm. Hg. The lungs were clear. The heart was "enlarged," the pulse rate was 74 per minute, and the rhythm was regular. A slight "systolic murmur" was audible at the apex. Blood chemistry, blood count, urinalysis, and serology were all negative. X-ray showed an enlarged left ventricle. An electrocardiogram on March 26, 1957, revealed "regular sinus rhythm, pattern of left ventricular hypertrophy, and right bundle branch block."

On Sept. 6, 1957, she had an episode of unconsciousness, which was sudden in onset and lasted for 10 minutes. The electrocardiogram at this time showed complete A-V dissociation and posterolateral wall ischemia. During the next few days the pulse rate ranged between 48 and 32 per minute.

On Sept. 18, 1957, she was transferred to the Hospital Division. Her cardiac rate was now 36 per minute. She was in no distress. The electrocardiogram now revealed A-V block, 2:1, 3:1, with periods of complete A-V dissociation, ventricular bigeminy, and changes suggestive of anteroseptal wall infarction.

From the Brooklyn Hebrew Home and Hospital for the Aged, Brooklyn, N. Y.
Received for publication May 23, 1959.

TABLE I. RELATION OF MAGNITUDE* OF THE T WAVE AND DURATION OF THE PRECEDING DIASTOLIC PERIOD (TRACING OF SEPT. 21, 1957, CYCLES 5 TO 9)

	NUMBER OF CYCLE				
	5	6 ES	7	8 ES	9
Duration† of preceding diastole (1/100 sec.)	105	—	108	—	108
Voltage of T wave (mm.)					
Upright	—	—	—	—	—
Inverted	16.25	—	17	—	17

*Because of a downsloping base line the beginning of the QRS was used as the reference level for the measurements of the T in all tracings. The voltage was measured to the nearest 0.25 mm.
†Time measurements are given in 1/100 second.

TABLE II. RELATION OF MAGNITUDE OF THE T WAVE AND DURATION OF THE PRECEDING DIASTOLIC PERIOD (TRACING OF SEPT. 21, 1957, CYCLES 34 TO 45)

	NUMBER OF CYCLE											
	34	35	36	37	38	39	40	41	42	43	44	45
Duration of preceding diastole (1/100 sec.)	†	100	70	*	28	92	72	*	28	12	16	14
Voltage of T wave (mm.)												
Upright	—	—	—	3.5	—	—	—	3.5	—	—	—	—
Inverted	12.5	17.25	15.5	1	13	17	16	1	13.5	11	12.5	11.5

*Not discernible.
†Not ascertainable.

TABLE III. RELATION OF MAGNITUDE OF THE T WAVE AND DURATION OF THE PRECEDING DIASTOLIC PERIOD (TRACING OF SEPT. 21, 1957, CYCLES 17 TO 21)

	NUMBER OF CYCLE				
	17	18 ES	19	20	21
Duration of preceding diastole (1/100 sec.)	*	—	40	<4	24
Voltage of T wave (mm.)					
Upright	—	—	—	—	—
Inverted	18.5	—	15	4	14

*Not ascertainable.

Since there were no syncopal attacks, both Isuprel and digitalis were withdrawn after two weeks. She improved progressively, and by Oct. 31, 1957, she was ambulant, with a pulse rate of 72 per minute.

On Feb. 7, 1958, she suffered another syncopal attack, with a drop of the heart rate to 40 beats per minute. She improved on Isuprel, and by Feb. 24, 1958, the extrasystoles noted previously had disappeared, but the heart rate continued at 42 per minute.

On March 30, 1958, she developed sudden dyspnea and cyanosis, rallying briefly, only to expire in an episode of dyspnea the same day.

A tracing taken on Sept. 19, 1957 (Fig. 1) shows second degree A-V block with varying ventricular response of 2:1, 3:1, and more. Ventricular extrasystoles were recorded singly, forming ventricular bigeminy, and in series of two and more.

The most prominent feature of the electrocardiogram is the presence of huge and wide inverted T waves, registered in Leads V_4 to V_6. The widening is accentuated by the merging of the final limb of the T wave with the U wave and the superposition of the P wave. The Q-T interval is obviously and grossly prolonged. Its exact duration cannot be determined because of the distortion of its terminal portion. The extrasystoles constituting the bigeminy occur on the upstroke of the T wave, following the inscription of the P wave. The succeeding auricular impulse is usually blocked, giving rise to a 3:1 block. This suggests retrograde conduction of the extrasystole. When two and, usually, when three extrasystoles were inscribed in succession, the 3:1 block persisted, suggesting retrograde conduction of only the first extrasystoles.

TABLE IV. RELATION OF MAGNITUDE OF THE T WAVE AND DURATION OF THE PRECEDING DIASTOLIC PERIOD (TRACING OF SEPT. 23, 1957, CYCLES 1 TO 10)

	NUMBER OF CYCLE									
	1	2	3 ES	4	5	6	7	8	9	10
Duration of preceding diastole (1/100 sec.)	*	128	—	56	24	36	124	24	34	120
Voltage of T wave (mm.)										
Upright	—	—	—	—	—	—	—	—	—	—
Inverted	12.5	15	—	15.25	13	13	15.75	12.25	13	15.5

*Not ascertainable.

A tracing taken two days later (Sept. 21, 1957) shows further improvement in the function of the A-V conduction system. Periods of regular sinus rhythm, of three to six beats, alternate with periods of 3:1 and 2:1 transmission. Ventricular extrasystoles are less numerous. As a consequence of these variations in rhythm the duration of the diastolic period fluctuates widely. Associated with these fluctuations are marked alterations in the amplitude, shape, and direction of the T waves. Thus, T waves ranging from 18 mm. in depth to a few millimeters in height were recorded (Figs. 2, 3, and 4). Tables I, II, and III, corresponding to these figures, show the relationship between the amplitude of the T wave and the length of the preceding diastolic period.

In connection with Figs. 2 to 4, certain observations are in order: (1) In general, in this case, giant T waves as recorded in Cycle 35 were inscribed whenever the diastole approached 100. (2) Cycles 42 to 45 illustrate alternation of the size of the T wave and corresponding alternation in the duration of the Q-T interval. Such alternations were noted whenever series of sinus rhythm of more than four beats were recorded. (3) In each series of sinus rhythm the T wave of the second beat was most strongly affected by the sudden change in the cardiac rate. The degree of change in the configuration depends on the duration of the preceding diastolic period. Whenever a giant T wave (Cycle 35 in Fig. 3) precedes a series, the T wave of the first beat fills the entire

cycle from the S-T junction to the onset of the subsequent QRS complex, leaving only a minimal diastolic period, if any. The T wave of the second beat shows the pattern of ischemia-injury (Cycle 37 or 41); its QRS is slightly modified. In those instances in which the sinus series is preceded by the compensatory pause of a ventricular extrasystole, the T wave of the first beat is of somewhat shorter duration, leaving a discernible diastole. The T wave of the second beat is small and of the coronary type (Cycle 20).

Another two days later (Sept. 23, 1957) regular sinus rhythm was established. Periods of 2:1 block were encountered only rarely. On one occasion several periods of block were recorded at short intervals. This is shown in Fig. 5 and Table IV. As can be seen, the T waves of the regular beats are sharply inverted, the Q-T interval smaller than in cycles with comparable T waves on the previous record. The T waves following the periods of block, and those following the shorter compensatory pause of a ventricular extrasystole are of identical contour and deeper than the T waves of the other regular beats. This is in distinct contrast to the marked variation in the size of the T waves with varying duration of the preceding diastolic period observed in the previous record.

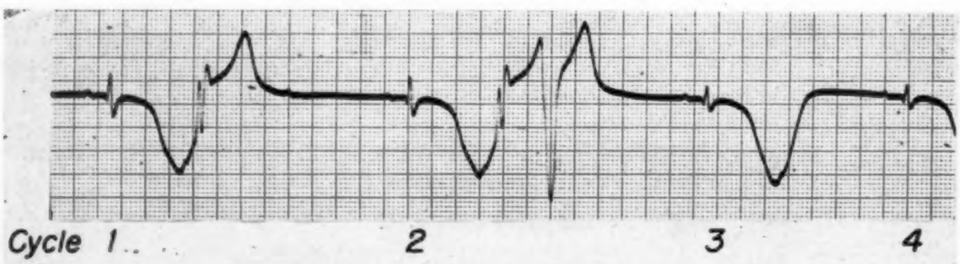

Fig. 1.—A continuous strip of Lead V_4 of the tracing taken on Sept. 19, 1957. The tracing shows giant negative T waves in sinus beats. The P waves are regularly spaced at an interval of 82 (1/100 sec.), corresponding to a rate of 73 per minute. A ventricular extrasystole follows the first conducted sinus beat, and two successive extrasystoles follow the second one. No extrasystole is interposed between the third and fourth conducted sinus beats. The R-R intervals of the sinus beats measure 254 (3 × 82), 254 (3 × 82), and 168 (2 × 82), respectively, indicating the presence of 3:1 block when a single extrasystole and two successive extrasystoles occurred, and 2:1 block in the absence of an extrasystole.

COMMENT

Massive T-wave inversion in coronary heart disease has been the subject of various reports. Huge T waves were observed in cases with slow ventricular rate, and the possibility that increased and varying vagal tone plays a role in the mechanism of massive inversion was considered.[4] Some cases did not show slowing of the ventricular rate.[5] The authors felt that ischemia may have been a precipitating factor.

In our case the huge inverted T waves shown in Fig. 1 occur at a slow ventricular rate resulting from myogenic disturbance in the A-V system. The fact that huge T waves occur only after long diastolic periods, and the orderly and related manner of their variation, suggest that the extent of the prolongation of diastole and the consequently increased filling of the heart is a determining factor in the production of the T-wave changes. In the opinion of Scherf[1] "alterations of the T waves seem to be chiefly connected with changes in the filling of the heart," and again, "the different metabolic processes accompanying alteration of the contractility seem to be the most probable explanation for the changes in the T

waves as described. It is conceivable that changes in the strength of systole are unaccompanied by changes in the form of the T wave under normal conditions, but appear if the heart is in some way 'damaged'." As observed in this case, the giant T waves in the second electrocardiogram (Figs. 2-4) appear to have been merely a specific alteration which occurred in the then existing state of the myo-

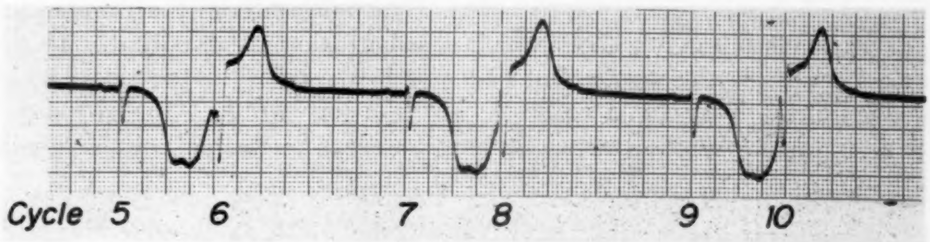

Fig. 2.—A strip of Lead V_4 of the tracing taken on Sept. 21, 1957. The figure shows giant negative T waves in sinus beats when following prolonged diastolic periods.

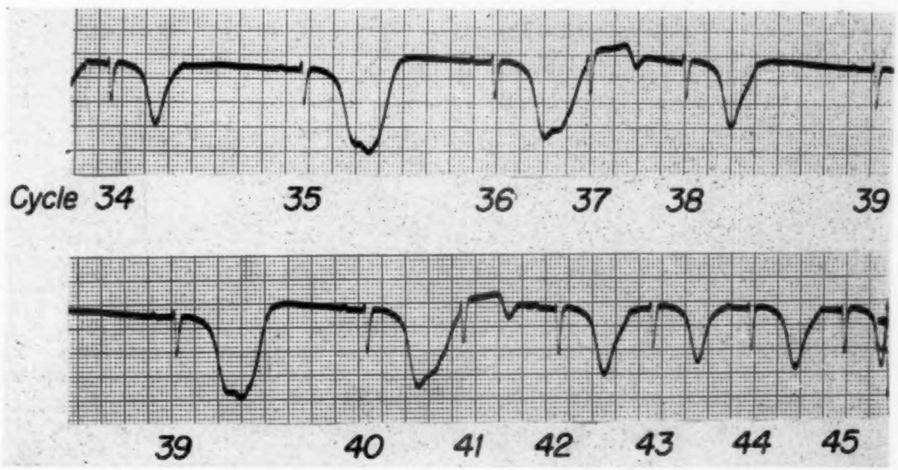

Fig. 3.—The two strips are continuous records of Lead V_4 of the same tracing shown in Fig. 2. The last beat—Cycle 39—of the upper strip is reproduced at the start of the lower strip. The figure illustrates the marked alterations of the T waves subsequent to diastolic periods of various duration, and the almost identical contour when they follow diastolic periods of the same duration.

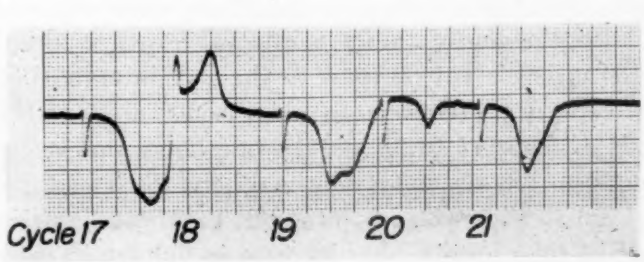

Fig. 4.—A strip of Lead V_4 of the same tracing shown in Figs. 2 and 3. The figure illustrates the alterations of the T waves subsequent to the compensatory pause of a ventricular extrasystole.

cardium in response to marked lengthening of the diastole and increased filling of the heart. It is generally accepted that in ischemia of the subepicardial myocardium the electrical activity is prolonged in these layers, resulting in inversion of the T wave and prolongation of the Q-T interval.[6] Since the T waves are less wide and deep in the third electrocardiogram (Fig. 5) that in the previous one, it may be assumed that the circulation in the vicinity of the infarcted area had improved when this tracing was recorded. The uniformity of the T waves following diastolic periods of markedly varying prolongation suggests that with a lesser degree of ischemia the myocardium became less susceptible to variations in the diastolic filling. This is in accordance with the concept of Levine and associates[2] that alterations in postextrasystolic beats suggest "ischemia" or "ischemia-like changes."

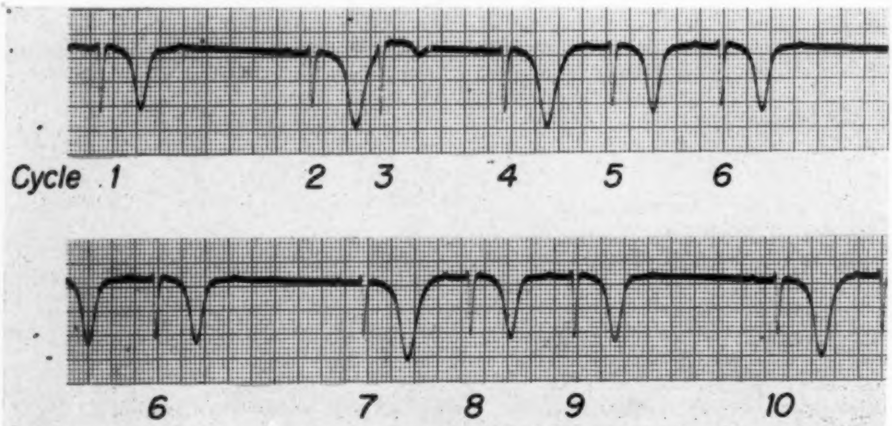

Fig. 5.—The two strips are continuous records of Lead V_5 of the tracing taken on Sept. 23, 1957. The last cycle of the upper strip—Cycle 6—is reproduced at the start of the lower strip. The figure illustrates the alterations of the T waves following each of the prolonged periods of block, and those following the compensatory pause of a ventricular extrasystole.

As was noted, alternate changes in the size of the T waves in regular sinus rhythm occurred whenever sinus series of more than four beats were recorded. Alternans of the T wave per se is physiologic. It occurs when the cardiac rate is suddenly accelerated, and is the effect of the sluggish adaptation of the recovery phase to the new rate.[7,8] Under physiologic conditions the T wave maintains its contour, while its duration undergoes variations—as evidenced by the alternate shortening and lengthening of the Q-T interval—until equilibrium is reached. In our case, alternation is not confined to the Q-T interval, but extends to the size of the T. Table V presents data (taken from Tables I-III) for cycles with diastolic periods of from 12 to 28, on the one hand, and cycles with diastolic periods of from 92 to 108 and more, on the other. This juxtaposition hints at a relatively much greater increase in voltage in the diastolic periods in the range between 12 and 28 than for a similar increase in voltage in the diastolic periods in the range of values above 92. This may be explained by the rapid filling of the ventricles in early diastole, in which a small increment in duration is associated

with a large increase in filling, whereas at the end of a prolonged diastole the opposite occurs. This would support the viewpoint that the variations in the T waves are the response of the ischemic myocardium to changes in filling.

The strikingly small T wave, of the coronary type (as illustrated in Cycle 20), measures half the voltage of the T's almost adapted to the new rate. The Q-T interval is shorter than that of the subsequent beat by one fifth. The pronounced reduction in the Q-T interval in our case is not merely part of the adaptation process.[9] Such shortening has been attributed to marked acceleration in the electrical activity in both the subendocardial and subepicardial layers, and has been observed in experimental asphyxia in cats and during pure nitrogen breathing.[10]

The ventricular complex following an imperceptible diastolic period (illustrated in Cycles 39 or 41) shows, in addition to the disproportionally short Q-T interval, elevation of the S-T segment and terminal inversion of the T wave. The QRS complex is slightly modified. Although restricted to three cycles only, the change has the earmarks of alternans of the S-T segment. This phenomenon is thought to be due to failure of parts of the ventricular muscle to depolarize. Alternation of the S-T segment is commonly observed in experimental occlusion and indicates severe myocardial damage.[7] Experimental findings and clinical experience point up the fact that transient displacement of the S-T segment,[11,12] even with transient modification, simulating myocardial infarction may result from extreme coronary insufficiency. The changes in the T wave, and those of the entire ventricular complex observed in the second cycle of each sinus series may be analogously related to extreme reduction in the coronary flow.

TABLE V. JUXTAPOSITION OF SOME DATA OF TABLES I-III, ARRANGED IN ORDER OF INCREASING MAGNITUDE

DURATION OF PRECEDING DIASTOLE (1/100 SEC.)	RANGE OF VOLTAGE OF T WAVE (MM.)	DURATION OF PRECEDING DIASTOLE (1/100 SEC.)	RANGE OF VOLTAGE OF T WAVE (MM.)
12	11	92	17
16	11.5	100	17.25
24	12.5-14	105	16.25
28	13-13.5	108	17
		108	17
		>110	18.5

CONCLUSION AND SUMMARY

1. Three electrocardiograms in a case of recent myocardial infarction are presented. The tracings were taken at two-day intervals. The first shows giant T waves, and the second and third show variations of the T waves in the presence of partial heart block.

2. Analysis revealed progressive enlargement of the T waves with increasing length of the preceding diastole. At one end of this progression are the small T

waves of short duration, with and without displacement of the S-T segment, which follow small or imperceptible diastoles; at the other end are the giant T waves which follow long periods of block.

3. The different behavior of T waves following diastoles of similar duration in the second and third electrocardiograms suggests improvement of the circulation on the latter occasion. This different behavior supports the opinion that in the second electrocardiogram the increase in the size of the T waves with increasing length of the preceding diastole demonstrated the response of the ischemic myocardial layers to the increased filling of the heart.

4. When the diastole was shortened to a point at which it was barely or not at all discernible, changes in the subsequent T wave or the entire ventricular complex were observed and may have been related to severe coronary insufficiency analogous to experimental and clinical experience.

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